

EMERGING HEALTH CARE ISSUES: FOLLOW-ON BIOLOGIC DRUG COMPETITION

HEARING BEFORE THE SUBCOMMITTEE ON HEALTH OF THE COMMITTEE ON ENERGY AND COMMERCE HOUSE OF REPRESENTATIVES ONE HUNDRED ELEVENTH CONGRESS FIRST SESSION

JUNE 11, 2009

Serial No. 111-46



Printed for the use of the Committee on Energy and Commerce
energycommerce.house.gov

U.S. GOVERNMENT PRINTING OFFICE

73-747 PDF

WASHINGTON : 2012

For sale by the Superintendent of Documents, U.S. Government Printing Office
Internet: bookstore.gpo.gov Phone: toll free (866) 512-1800; DC area (202) 512-1800
Fax: (202) 512-2104 Mail: Stop IDCC, Washington, DC 20402-0001

COMMITTEE ON ENERGY AND COMMERCE

HENRY A. WAXMAN, California, *Chairman*

JOHN D. DINGELL, Michigan
Chairman Emeritus

EDWARD J. MARKEY, Massachusetts
RICK BOUCHER, Virginia
FRANK PALLONE, JR., New Jersey
BART GORDON, Tennessee
BOBBY L. RUSH, Illinois
ANNA G. ESHOO, California
BART STUPAK, Michigan
ELIOT L. ENGEL, New York
GENE GREEN, Texas
DIANA DeGETTE, Colorado

Vice Chairman

LOIS CAPPS, California
MICHAEL F. DOYLE, Pennsylvania
JANE HARMAN, California
TOM ALLEN, Maine
JANICE D. SCHAKOWSKY, Illinois
CHARLES A. GONZALEZ, Texas
JAY INSLEE, Washington
TAMMY BALDWIN, Wisconsin
MIKE ROSS, Arkansas
ANTHONY D. WEINER, New York
JIM MATHESON, Utah
G.K. BUTTERFIELD, North Carolina
CHARLIE MELANCON, Louisiana
JOHN BARROW, Georgia
BARON P. HILL, Indiana
DORIS O. MATSUI, California
DONNA CHRISTENSEN, Virgin Islands
KATHY CASTOR, Florida
JOHN P. SARBANES, Maryland
CHRISTOPHER S. MURPHY, Connecticut
ZACHARY T. SPACE, Ohio
JERRY McNERNEY, California
BETTY SUTTON, Ohio
BRUCE BRALEY, Iowa
PETER WELCH, Vermont

JOE BARTON, Texas
Ranking Member

RALPH M. HALL, Texas
FRED UPTON, Michigan
CLIFF STEARNS, Florida
NATHAN DEAL, Georgia
ED WHITFIELD, Kentucky
JOHN SHIMKUS, Illinois
JOHN B. SHADEGG, Arizona
ROY BLUNT, Missouri
STEVE BUYER, Indiana
GEORGE RADANOVICH, California
JOSEPH R. PITTS, Pennsylvania
MARY BONO MACK, California
GREG WALDEN, Oregon
LEE TERRY, Nebraska
MIKE ROGERS, Michigan
SUE WILKINS MYRICK, North Carolina
JOHN SULLIVAN, Oklahoma
TIM MURPHY, Pennsylvania
MICHAEL C. BURGESS, Texas
MARSHA BLACKBURN, Tennessee
PHIL GINGREY, Georgia
STEVE SCALISE, Louisiana

SUBCOMMITTEE ON HEALTH

FRANK PALLONE, JR., New Jersey, *Chairman*

JOHN D. DINGELL, Michigan
BART GORDON, Tennessee
ANNA G. ESHOO, California
ELIOT L. ENGEL, New York
GENE GREEN, Texas
DIANA DeGETTE, Colorado
LOIS CAPPS, California
JAN SCHAKOWSKY, Illinois
TAMMY BALDWIN, Wisconsin
MIKE ROSS, Arkansas
ANTHONY D. WEINER, New York
JIM MATHESON, Utah
JANE HARMAN, California
CHARLES A. GONZALEZ, Texas
JOHN BARROW, Georgia
DONNA M. CHRISTENSEN, Virgin Islands
KATHY CASTOR, Florida
JOHN P. SARBANES, Maryland
CHRISTOPHER S. MURPHY, Connecticut
ZACHARY T. SPACE, Ohio
BETTY SUTTON, Ohio
BRUCE L. BRALEY, Iowa

NATHAN DEAL, Georgia,
Ranking Member
RALPH M. HALL, Texas
BARBARA CUBIN, Wyoming
HEATHER WILSON, New Mexico
JOHN B. SHADEGG, Arizona
STEVE BUYER, Indiana
JOSEPH R. PITTS, Pennsylvania
MARY BONO MACK, California
MIKE FERGUSON, New Jersey
MIKE ROGERS, Michigan
SUE WILKINS MYRICK, North Carolina
JOHN SULLIVAN, Oklahoma
TIM MURPHY, Pennsylvania
MICHAEL C. BURGESS, Texas

CONTENTS

	Page
Hon. Frank Pallone, Jr., a Representative in Congress from the State of New Jersey, opening statement	1
Hon. Nathan Deal, a Representative in Congress from the State of Georgia, opening statement	3
Hon. Henry A. Waxman, a Representative in Congress from the State of California, opening statement	4
Prepared statement	7
Hon. Ed Whitfield, a Representative in Congress from the Commonwealth of Kentucky, opening statement	12
Hon. Anna G. Eshoo, a Representative in Congress from the State of California, opening statement	12
Hon. Michael C. Burgess, a Representative in Congress from the State of Texas, opening statement	14
Hon. John D. Dingell, a Representative in Congress from the State of Michigan, opening statement	15
Hon. Marsha Blackburn, a Representative in Congress from the State of Tennessee, opening statement	17
Hon. Jim Matheson, a Representative in Congress from the State of Utah, opening statement	18
Hon. Phil Gingrey, a Representative in Congress from the State of Georgia, opening statement	19
Hon. Jane Harman, a Representative in Congress from the State of California, opening statement	20
Hon. Joseph R. Pitts, a Representative in Congress from the Commonwealth of Pennsylvania, opening statement	20
Hon. Donna M. Christensen, a Representative in Congress from the State of Virgin Islands, opening statement	21
Hon. Steve Buyer, a Representative in Congress from the State of Indiana, opening statement	22
Hon. Gene Green, a Representative in Congress from the State of Texas, opening statement	23
Hon. John Shimkus, a Representative in Congress from the State of Illinois, opening statement	24
Hon. Tammy Baldwin, a Representative in Congress from the State of Wisconsin, opening statement	24
Hon. Tim Murphy, a Representative in Congress from the Commonwealth of Pennsylvania, opening statement	25
Hon. Zachary T. Space, a Representative in Congress from the State of Ohio, opening statement	26
Hon. Betty Sutton, a Representative in Congress from the State of Ohio, opening statement	26
Hon. Bruce L. Braley, a Representative in Congress from the State of Iowa, opening statement	27
Hon. Janice D. Schakowsky, a Representative in Congress from the State of Illinois, opening statement	28
WITNESSES	
Pamela Jones Harbour, Commissioner, Federal Trade Commission; and Michael Wroblewski, Deputy Director of the FTC's Office of Policy Planning	29
Prepared statement	33
Answers to submitted questions ¹	

VI

	Page
SUBMITTED MATERIAL	
Federal Trade Commission report of June 2009	40
Working paper by Duke University Department of Economics on Data Exclu- sivity, dated December 22, 2008, submitted by Mr. Buyer	184
HHS responses to subcommittee, dated September 18, 2008, submitted by Ms. Eshoo	234
Report entitled, "Proper Duration of Data Exclusivity for Generic Biologics," by Alex M. Brill, submitted by Mr. Deal	250
Report entitled, "Stimulating Innovation in the Biologics Industry: A Bal- anced Approach to Marketing Exclusivity," by Laurence J. Kotlikoff, sub- mitted by Mr. Deal	262
Report entitled, "Biologics in Perspective: The Case for Generic Biologic Drugs," by AARP Public Policy Institute, submitted by Mr. Deal	282

¹ Ms. Harbour did not respond to submitted questions for the record.

EMERGING HEALTH CARE ISSUES: FOLLOW- ON BIOLOGIC DRUG COMPETITION

THURSDAY, JUNE 11, 2009

HOUSE OF REPRESENTATIVES,
SUBCOMMITTEE ON HEALTH,
COMMITTEE ON ENERGY AND COMMERCE,
Washington, DC.

The Subcommittee met, pursuant to call, at 10:08 a.m., in Room 2123 of the Rayburn House Office Building, Hon. Frank Pallone, Jr. [chairman of the subcommittee] presiding.

Present: Representatives Pallone, Dingell, Gordon, Eshoo, Green, DeGette, Capps, Schakowsky, Baldwin, Matheson, Harman, Barrow, Christensen, Castor, Sarbanes, Murphy of Connecticut, Space, Sutton, Braley, Waxman (ex officio), Deal, Whitfield, Shimkus, Buyer, Pitts, Myrick, Murphy of Pennsylvania, Burgess, Blackburn, and Gingrey.

Also present: Representative Inslee.

OPENING STATEMENT OF HON. FRANK PALLONE, JR., A REPRESENTATIVE IN CONGRESS FROM THE STATE OF NEW JERSEY

Mr. PALLONE. The meeting of the subcommittee is called to order, and I will recognize myself initially. Today, the subcommittee is meeting to discuss the Federal Trade Commission report entitled Emerging Health Care Issues: Follow-on Biologic Drug Competition. This is an extremely timely report and goes to the very heart of our President and this Congress' commitment to ensuring affordable and quality health care for every American. Creating a statutory pathway for the approval of follow-on biologics presents us with an opportunity to improve millions of lives at a more affordable cost. Currently, brand biologics account for approximately 15 percent of total U.S. prescription drug sales, and the industry is growing at a rate of around 20 percent annually. In a couple years, we could be spending over \$100 billion just on biologic drugs.

According to data from the Centers for Medicare and Medicaid Services, CMS, just 4 biologics account for 30 percent of all Medicare Part B spending. Obviously, these drugs are costing the health care system a lot of money, and it is not just the health system that is being burdened by these high costs. For American families biologics can cost in the tens of thousands of dollars for the most popular drugs. In some cases the life-saving biologic can cost a patient over \$300,000 a year. There is no doubt that these innovative drugs provide Americans access to ground breaking treatments for

devastating illnesses, including cancer, arthritis, and multiple sclerosis.

But I have heard too many stories from my home district in New Jersey and from all around the country of hard-working people who just can't afford the tremendous cost of these life-saving and life-improving drugs. In a country of the best and the brightest, which we are, I have to believe that we can do better. We must continue to innovate and push the envelope to discover more effective treatments and cures for the scourges of our time. In the same vein, we must also ensure that these innovative products are available to patients at an affordable price. We are faced with a delicate balance moving forward between ensuring reasonable drug prices and expenditures, increasing access for more Americans, and supporting innovation. And I know that we have different bills on this subject and we have significant disagreements, but I also think that we all believe that we need to move forward with a pathway for these follow-on biologics, and this hearing today is the beginning of that process.

There are some principles, the same principles that essentially guided us with chemical substances I think can guide us in the creation of legislation today. We all know about the Hatch-Waxman Act. Mr. Waxman isn't here, but I am sure he will be.

Mr. WAXMAN. I am.

Mr. PALLONE. Oh, you are. I am sorry.

Mr. WAXMAN. It is Waxman-Hatch.

Mr. PALLONE. Yes, I know. I was going to say that. I see in the document it says Hatch-Waxman. I said it is Waxman-Hatch, not Hatch-Waxman. But we know that Waxman-Hatch has been a great success since its passage or since it went into effect in 1984. And since its passage more generic drug manufacturers have entered the market driving down costs to the consumer. Also, pioneer drug companies have given protections that have spurred innovation leading to advancements that are helping us to live longer and healthier lives. In addition to driving innovation, Waxman-Hatch was also able to effectively and without any market interference drive down the cost of drugs. In fact, the U.S. health care system has saved over \$700 billion in the past 10 years through the use of generic pharmaceuticals. In a time when we are facing an economic crisis partly brought on by skyrocketing health care costs, this is a staggering figure.

If biologics are the future, then we should do everything we can now to control costs while aiding innovation just like Waxman-Hatch did. So today we are hearing testimony on the newly-released Federal Trade Commission report looking specifically at the issues of innovation, cost, and competition. The FTC has decades of expertise in this area and I value their objective and comprehensive analysis. I am anxious to hear from the FTC about what factors we must consider when moving forward with legislation and how follow-on biologics are likely to behave in the market setting as compared to generics. I am especially curious to hear about what incentives and protections will be necessary in a biologic and follow-on biologic world that are similar or different than the current brand and generic arena.

And I want to welcome FTC Commissioner Harbour to the committee today. She comes from the State of New Jersey. Thank you for coming to testify before us. I would also like to welcome the author of the FTC report, Michael Wroblewski, who has been invited along with the Commission to answer more technical questions about the report. So thank you both for being here. I now recognize Mr. Deal for 5 minutes.

OPENING STATEMENT OF HON. NATHAN DEAL, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF GEORGIA

Mr. DEAL. Thank you, Chairman Pallone, for holding this hearing today on the issue of surrounding the establishment of an approval pathway and of patent protection concerns on follow-on biologics at the Food and Drug Administration and the resulting impact that this may have on competition and innovation in the biologic drug marketplace. I also want to thank Commissioner Harbour for joining us today to discuss the results of the Commission's very recently completed report. I look forward to that testimony and to the questions and answers that will follow regarding that report, and we hope she will be able to provide us some definition to the debate that currently surrounds this issue. As this subcommittee prepares to consider fundamental health reform this summer, I believe a critical component of such reform must include the establishment of appropriately abbreviated approval processes for follow-on biologic drugs, a priority upon which innovators engineers, and manufacturers both agree.

In 2007, global sales of biologic drugs reached \$75 billion, and current estimates suggest that over half of all drugs, both chemical and biologic in nature, will be bio-pharmaceutical products next year. Biologic drugs have provided some of the most promising benefits for a wide range of diseases, including anemia, hemophilia, cancer, diabetes, HIV, rheumatoid arthritis, and other debilitating medical conditions that affect millions of Americans every day. Access to lower cost biologics represents a critical step forward in reducing the overall high cost of health care and will provide greater access to patients in need of these critical life-saving therapies. In doing so, Congress must be certain a balanced approach is established, which encourages new innovation in new bio-pharmaceuticals while providing more affordable options for the American people.

At the center of this issue, the period of marked exclusivity given to innovator products, as well as patent dispute resolution procedures, and the flexibility which Congress will give to FDA to approve bio-similars will direct our nation's ability to expound upon the advancements in the biologic arena and to serve a growing number of patients in dire need of these drugs. In the report under consideration today produced by the Federal Trade Commission, a number of arguments are made which support the robustness of our current patent system as it applies to biologics and highlights the question how long of a period of market exclusivity must an innovator of biologic products be afforded in order to yield net profit results, notably with respect to the significant outlays expended in bringing the product to market and how the current intellectual property rights translate into the field of bio-pharmaceuticals.

I recognize the critical need for innovators to earn a profit on innovative and cutting edge therapies, but also recognize the importance of ensuring access to the American people who simply cannot gain access to these critical therapies solely based upon their significant cost. Therefore, a delicate balancing act must be played as we pursue congressional establishment of an appropriate approval pathway and patent resolution processes under FDA for these unique drugs. Among the report's findings, I am particularly interested in the stated dynamic of competition which follow-ons are likely to face upon an appropriate approval mechanism once it is in place. According to the report, pioneer manufacturers, potential follow-on biologic manufacturers, and payors were virtually unanimous in their predictions that competition from follow-on biologic drug entry is likely to resemble brand to brand competition rather than brand to generic drug competition.

And unlike chemical generic drug entry, follow-on biologic entry would not result in steep price discounting or rapid acquisition of market share by follow-on biologic manufacturers. Therefore, although the introduction of a bio-similar may result in a 10 to 30 percent reduction in innovator price and an introduction of a competing product into the marketplace innovator companies are still capable of securing adequate positive returns on investment for years to come and maintain significant market share. And it is important to note the exorbitant cost of many of these therapies which thousands of Americans across the country are forced to accept. For example, taking a conservative 15 percent reduction in cost of a hypothetical follow-on bio-pharmaceutical which would cost \$40,000 per year. Allowing bio-similars into the marketplace could potentially save this individual \$6,000 per year, which is a dramatic step toward reigning in the cost of these drugs while encouraging innovation.

There are a lot of questions which remain. I remain committed to working on this issue, an issue which I do believe cannot wait any longer to be addressed. I appreciate the cooperation of my colleagues on this committee. I look forward to the testimony. I look forward to working together cooperatively as we move this issue forward. Thank you, Mr. Chairman.

Mr. PALLONE. Thank you, Mr. Deal, and thank you for prioritizing this issue. And now the chairman, Mr. Waxman.

OPENING STATEMENT OF HON. HENRY A. WAXMAN, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF CALIFORNIA

Mr. WAXMAN. Thank you very much, Mr. Chairman. Today, we are going to hear from the Federal Trade Commission on an issue of paramount importance to the debate on a pathway for approval of follow-on biologics, how long a period of exclusive marketing must we give to biotech drugs to sustain innovation. As was true when Congress passed the Hatch-Waxman Act 25 years ago, an effective follow-on biologics bill must maintain a balance between increasing consumer access to affordable medicines on the one hand and providing adequate incentives for innovation on the other. Life-saving drugs are useless if no one can afford them, yet making today's drugs affordable does us little good if we cut off the supply

of future breakthroughs. We have made great progress in the last 3 years toward a consensus on how to ensure that follow-on biologics are safe and effective. Just 2 years ago the drug industry argued that it was impossible to make follow-on biologics. Now there is agreement that it can be done.

But we remain divided on what incentives are needed for innovation. It is no longer a matter of whether patients will get generic versions of these life-saving medicines but when. In assessing how much exclusive marketing is needed to sustain innovation, I began with a basic premise. The balance we struck in the Hatch-Waxman Act has worked well for 25 years. It has given us access to affordable drugs and it has not damaged innovation. Pharmaceutical R&D expenditures have not just been maintained, but have steadily risen throughout these 25 years. Under Waxman-Hatch innovative drugs get 5 years of exclusivity. The drug industry has been engaged in a massive and expensive lobbying campaign to convince the members of this committee that the supply of life-saving drugs will dry up if they don't get triple the monopoly protection available to all other drugs. The drug industry is demanding 12 or even 14 years of exclusivity for biotech drugs.

To support this extraordinary request, the industry makes 2 main arguments. First, that their patents are much weaker than drug patents and won't block competition from follow-ons. Second, that it takes 12 to 16 years for biotech drugs to break even so that is the period of exclusivity they need. Though I have seen little or no persuasive evidence to support these arguments, the industry has blanketed Capitol Hill with them. The outcome of this debate is too important for our nation's health to let lobbying cloud decisions. The cost of reaching the wrong decision is simply too high. Instead, the appropriate length of exclusivity must be decided on the basis of evidence and analysis by objective experts, experts who are not being paid by one side or the other. That is why I am so pleased that the Federal Trade Commission has undertaken an in-depth review of all the evidence and arguments on both sides of this debate. The FTC employs economists, patent lawyers, and experts in the pharmaceutical marketplace. Their job is to assess the impact of laws, regulations, and marketing practices on both competition and innovation in the prescription drug marketplace.

The FTC has overseen this marketplace for decades and has produced highly respected reports on generic drug competition and anti-competitive practices in the drug marketplace. For example, in 2002 the FTC produced a report on abuses of Hatch-Waxman that inappropriately delayed consumer access to generic drugs. The report resulted in important amendments to our law enacted the following year. Today, the FTC will tell us whether the methods we have used to sustain innovation in the drug industry, patents, and the market-based pricing with perhaps a short period of exclusivity are adequate to sustain innovation for biotech drugs, and they will tell us whether the argument is in favor of 12 to 14 years of exclusive marketing hold up to scrutiny. Objective evidence-based answers to these questions from the expert agency charged with overseeing competition and innovation of the drug marketplace will provide critical information to the committee as we move forward.

I look forward to exploring the FDC's analysis and conclusions on these questions. Thank you very much, Mr. Chairman.
[The prepared statement of Mr. Waxman follows:]

**Opening Statement of Rep. Henry A. Waxman
Chairman, Committee on Energy and Commerce
Emerging Health Care Issues: Follow-on Biologic Drug
Competition Subcommittee on Health
June 11, 2009**

Today we will hear from the Federal Trade Commission on an issue of paramount importance in the debate on a pathway for approval of follow-on biologics: How long a period of exclusive marketing we must give to biotech drugs to sustain innovation.

As was true when Congress passed the Waxman-Hatch Act 25 years ago, an effective follow-on biologics bill must maintain a balance between increasing consumer access to affordable medicines, on the one hand, and providing adequate incentives for innovation, on the other. Life-saving drugs are useless if no one can afford them. Yet, making today's drugs affordable does us little good if we cut off the supply of future breakthroughs.

We have made great progress in the last 3 years towards a consensus on how to ensure that follow-on biologics are safe and effective. Just 2 years ago, the drug industry argued that it was impossible to make follow-on biologics. Now there is agreement that it can be done.

But we remain divided on what incentives are needed for innovation. It's no longer a matter of whether patients will get generic versions of these life-saving medicines, but when.

In assessing how much exclusive marketing is needed to sustain innovation, I begin with a basic premise: the balance we struck in Waxman-Hatch has worked well for 25 years. It has given us access to affordable drugs and it has not damaged innovation. Pharmaceutical R&D expenditures have not just been maintained, but have steadily risen throughout those 25 years. Under Waxman-Hatch, innovative drugs get 5 years of exclusivity.

The drug industry has been engaged in a massive and expensive lobbying campaign to convince the members of this Committee that the supply of life-saving drugs will dry up if they don't get triple the monopoly protection available to all other drugs. The drug industry is demanding 12 or even 14 years of exclusivity for biotech drugs.

To support this extraordinary request, the industry makes two main arguments. First, that their patents are much weaker than drug patents and won't block competition from follow-ons. Second, that it takes between 12 and 16 years for biotech drugs to break even so that's the period of exclusivity they need. Though I have seen little or no persuasive evidence to support these arguments, the industry has blanketed Capitol Hill with them.

The outcome of this debate is too important for our nation's health to let lobbying clout decide it. The cost of reaching the wrong decision is simply too high. Instead, the appropriate length of exclusivity must be decided on the basis of evidence and analysis by objective experts. Experts who are not being paid by one side or the other.

That is why I am so pleased that the FTC has undertaken an in-depth review of all the evidence and argument on both sides of this debate. The FTC employs economists, patent lawyers, and experts in the pharmaceutical marketplace. Their job is to assess the impact of laws, regulations, and marketing practices on both competition and innovation in the prescription drug marketplace. The FTC has overseen this marketplace for decades and has produced highly-respected reports on generic drug competition and anti-competitive practices in the drug marketplace. For example in 2002, the FTC produced a report on abuses of Waxman-Hatch that inappropriately delayed consumer access to generic drugs. The report resulted in important amendments to Waxman-Hatch enacted the following year.

Today the FTC will tell us whether the methods we have always used to sustain innovation in the drug industry — patents, and market-based pricing, with perhaps a short period of exclusivity — are adequate to sustain innovation for biotech drugs. And they will tell us whether the arguments in favor of 12-14 years of exclusive marketing hold up to scrutiny.

The objective, evidence-based answers to these questions from the expert agency charged with overseeing competition and innovation in the drug marketplace will provide critical information to the Committee as we move forward.

I look forward to exploring the FTC's analysis and conclusions on these key questions.

Mr. PALLONE. Thank you, Chairman Waxman. Next is the gentleman from Kentucky, Mr. Whitfield.

OPENING STATEMENT OF HON. ED WHITFIELD, A REPRESENTATIVE IN CONGRESS FROM THE COMMONWEALTH OF KENTUCKY

Mr. WHITFIELD. Mr. Chairman, thank you very much for this important hearing today on an important subject matter. All of us are in total agreement that some type of generic pathway for biological drugs must be created. I think it demonstrates by the different bills that we have that there are some significant differences in how we create that pathway. We all understand yesterday that the Federal Trade Commission's report was submitted and it leaves many of us with some serious concerns with their findings, specifically the claim that data exclusivity is essentially unnecessary in a generic pathway. The scenario outlined by the FTC would, I believe, unfairly tilt competition in favor of bio-similars by allowing them to capitalize on innovators substantial research and development efforts at any time. This would create even more uncertainty, I believe, for innovators when they make their R&D decisions.

I might also say that Professor Dr. Henry Grabowski at Duke University, and you all can correct me if I am wrong on this, but I believe he has the only peer-reviewed document on this, and he summarized the findings of his study that concludes that without a data exclusivity period of between 13 and 16 years the future introduction of important new medicines could be delayed significantly or deterred altogether and that a strong innovative industry is necessary for an industry to thrive over the long term. So we find ourselves today trying to balance the need for new drugs providing low cost medicines for our senior citizens, and so this hearing is vitally important, and I certainly look forward to hearing from the Federal Trade Commission today and learning more about their report and how it compares with Dr. Grabowski's report. And thank you very much.

Mr. PALLONE. Thank you. Next is the gentlewoman from California, Ms. Eshoo, and I want to thank her also for all her work on this issue.

OPENING STATEMENT OF HON. ANNA G. ESHOO, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF CALIFORNIA

Ms. ESHOO. Thank you, Mr. Chairman, and good morning to everyone that is here. I am pleased to be here to discuss competition in the biotechnology industry, but I have to say that I am puzzled and somewhat disappointed by the subcommittee's approach to this critical issue. Everyone understands that this is not only critical, it is extremely complex. In May of 2007, over 2 years ago, the Health Subcommittee had a hearing on bio-similars. In October of 2007 subcommittee members met to discuss bio-similar, and the result of that meeting, as members might recall, was a series of questions that the members provided to stakeholders and the FDA several months later in April of 2008. We received thoughtful, thorough responses from a large number of interested organizations and experts.

Now today this is the first committee action on bio-similars in more than 2 years and a hearing on an FTC report we received less than 24 hours ago. When we were informed that there was going to be this hearing, we immediately called the FTC to ask for a copy of the report. They said that we could not have it, that it would be available the morning of the hearing. I then, Mr. Chairman, approached you and asked if members could at least see this the day before. Why have a hearing if you can't read the report that you are having the hearing on? So we did receive it. I don't know how many members have read this report, and I don't think that this process really reflects well on I think the most distinguished full committee and subcommittee in the House.

Now I assume that the FTC has devoted significant efforts and resources in putting this report together, but I am not convinced that the FTC Commission is—and what they have in this report are exactly what we have been waiting for 2 years to hear about. I have met with many scientists, doctors, patients, who have much to contribute to the subcommittee's deliberations, but we only have the FTC here today, and I guess it was the decision of the chairman not to have anyone else. This is a report that has not even had been subjected to the scrutiny of the public. I think that we can do better than that. Now what does the FTC report, as I read it as quickly as I could, what does it conclude? It says that increased competition in the biotechnology industry would result in lower prices for biologics. It is exactly why I introduced along with Mr. Inslee, Mr. Barton, the Pathway for Bio-Similars Act.

This is the Kennedy legislation in the House. Now competition is always healthy. Anyone that has known me over the 16-1/2 years I have been in the Congress knows that I believe that it benefits consumers whether it is in biotechnology, whether it is in telecommunications, whether it is in energy, whether it is health care, or whether it is baseball. I am a staunch advocate of fair competition and open markets, and I believe that my legislation will provide new competition while promoting sound science, and above all else protect patients. Any new pathway for bio-similars must provide effective safeguards for patients and sufficient incentives for the development of new treatments for the most deadly diseases that affect humankind today.

I am pleased that my bill enjoys the support of just shy of 100 members, bipartisan members, of the House, and it has received the endorsements of over 70 patient, physician, industry, and academic groups, as well as governors of 4 states. So I think that we need to be respectful of both efforts. And I am very proud of this because this is a complicated issue, and the amount of time spent with members, as well as members of the public and others, has been considerable. The establishment of a new regulatory pathway for approval of bio-similars is a critical matter for this subcommittee and the Congress to consider. I am eager to get to work on this, and I encourage you, Mr. Chairman, to hold more thorough and more inclusive hearings in the near future. I am glad that the FTC is here today. My understanding of the FTC is that most of its work deals with anti-trust. In my questions, I would like to know where the scientific data and the basis for the report has come from, but I nonetheless welcome the FTC here. You are an

important agency. And I thank you, Mr. Chairman, and I hope that when I ask you why we were doing it this way, your response was it is the only time we have before the August recess.

I think it could have been broader. I think the subcommittee deserves that. I think the full committee deserves that. I think the House of Representatives deserves that on this issue which is so critical, so critical, to the well-being of patients and a process by which we can reduce the cost of biologics for people in our country. So, thank you, and I yield back.

Mr. PALLONE. Thank you. And let me assure the gentlewoman, as I said, that we will have additional hearings on this very important issue.

Ms. ESHOO. When do you plan to do that?

Mr. PALLONE. Well, as I mentioned, we are going into the health care debate, so I can't say when, but I promise you we will because this is a very important issue for the members. Let me turn to the gentleman from Texas, Mr. Burgess.

**OPENING STATEMENT OF HON. MICHAEL C. BURGESS, A
REPRESENTATIVE IN CONGRESS FROM THE STATE OF TEXAS**

Mr. BURGESS. Thank you, Mr. Chairman. Mark me down as leaning ambivalent on this issue. Now just like everyone who sits on this committee, I know we have all spent months looking at the legislative proposals dealing with follow-on biologics. I know I personally have been in meeting after meeting with interested parties, and I have become convinced that this committee needs to hold more hearings. We lack sufficient information, primarily safety information, to render an informed opinion. We do have 2 bills championed by leaders on this committee, and we obviously need to explore those divergent points of view involved. Certainly, like Congresswoman Eshoo, I welcome Commissioner Harbour here. There are lots of things that I would like to discuss with the Federal Trade Commission. I am terribly interested in the lack of the ability of our physician community to be able to negotiate with our insurance community, but we don't get to do that today.

So my excitement with this hearing was tempered when I realized we really are only going to be focusing on a very narrow aspect of the bio-similars discussion, and that very narrow aspect will not include patient safety. Market exclusivity and patent integrity are important elements of any legislation authorizing a pathway for follow-on biologics. I was unaware that this committee had already achieved consensus on issues of safety, science, and the Food and Drug Administration. Assuming this committee has not reached such a consensus, then it is just downright frustrating that the Food and Drug Administration is not here in this room at this hearing. Now assuming that we didn't want to hold a series of hearings on points of disagreement and wanted our first focus to be on market forces, as we will today, then a second panel representing concurring or dissenting opinions from industry would be appropriate in my opinion.

And then maybe we could even hear from the scientists and the doctors. Mr. Chairman, I referenced last week I took a field trip out to the Food and Drug Administration last week. I had some wonderful interactions with some of the scientists who are working on

some of these very issues, the issues of bio-similars as they relate to monoclonal antibodies. This is the type of research that may unlock a lot of secrets that have been kept from our physician community for years, and it is just such terribly important information that I cannot believe we are going to be asked to make a decision without access to that information. I will be interested to what extent the Commissioner will be able to testify on the issue of interchangeability. Interchangeability is one of the foremost at issue of science, but it is importantly one of patient safety and that should have a physician and patient at the heart of the discussion.

I would not typically associate the Federal Trade Commission with such discussion. Mr. Chairman, I am fascinated by the prospect of a reliable, bio-similar pathway. Texas is becoming a focal point for bio-technology development. Not only does this mean new therapies for previously untreatable diseases with just the chance of projection that 50 percent of the drugs by 2020 will be biologics so this is a huge economic issue for Texas as well. Just as scientists and doctors have just scratched the surface of potential biologics for the next generation of cures and treatments, this committee has plenty of work to do to find a compromise bill that solidifies our ambitions and meets or exceeds our expectations. No artificial deadline, and this goes to the health reform debate as well, no artificial deadline should compel us to ride rough shod over the deliberative nature of this body in regular order. To do so not only tarnishes this great committee but could literally mean life or death for our constituents. Thank you, Mr. Chairman. I will yield back the balance of my time.

Mr. PALLONE. Thank you. The chairman emeritus, Mr. Dingell.

OPENING STATEMENT OF HON. JOHN D. DINGELL, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF MICHIGAN

Mr. DINGELL. Mr. Chairman, thank you, and I commend you for holding this hearing, which is very important. We are here to discuss the findings of the Federal Trade Commission with respect to its study on how competition between pioneer biologics and follow-on biologics is likely to develop. This is a series of hearings, which I hope will take place, which is wrought with many, many questions of great importance and many fewer answers of any relevance or importance. We have a tremendous opportunity here to develop a follow-on biologics policy that will bring the competition needed to provide greater access on life-saving biological drugs. However, we also have a responsibility to ensure that the innovation that develops the current biologic products continues in a way that will breed new effective therapies or a new group of conditions.

One thing the FTC report makes abundantly clear is that biologic products are different from small molecule chemical drugs. They are enormously complex, much longer, and they are also either products of or sometimes living organisms. The science is clearly different. The safety considerations between the 2 categories of drugs are different. And as the FTC report concludes, the competition between pioneer products and generic competitors is different. It must be noted that we will find that the traditional questions that FDA has had to address will be somewhat different

either in form or in total. And the question of whether it is safe, biologically equivalent, what are the side effects, contraindications, and whether it is effective are going to be interesting and different questions that have to be addressed.

It also is going to be a major question before us as to how we address the question of biological equivalency and whether or not one drug is an honest, safe substitute for another which could properly be prescribed with expectation of helping rather than hurting the patient. In 1984, Congress granted the FDA authority to approve generic drugs, and we all commend Chairman Waxman for his leadership in that effort. We did not foresee the need for a similar pathway for generic biologics. The science has exploded under our feet since then and in certain instances biotechnology provides clear technical advantages over other traditional therapies. We also need to examine if exclusivity limitations that we create is reflective of true costs in time and resources.

We also need to know how this is going to affect the cost of medicine and how it is going to impact on our efforts to reduce the tremendous skyrocketing now going on in health care costs. We also want consumers to make sure that there is affordable access to these life enhancing and sustaining therapies. What is the path forward on exclusivity? Is it 5 years, 12 years or 14 years, more or less? Eleven years the European has set forth. We need to create a framework that balances good science and the public health. We can also focus on patient safety and at the same time ensure that incentives remain for private innovation.

The FTC report does a good job of laying out the economic and competitive effects of a follow-on biologics policy. However, we should be reminded that safety should be our number 1 priority, and protection of the American consuming public should be of the highest priority. Policies that protect the safety of the patient is paramount as we forge ahead in the new area of follow-on biologics. We should be thoughtful as we move forward but not allow fear to restrict us, but above all else we have got to move forward to get the answers to the question. Here are a few questions that I find troublesome. What standards will ensure that follow-on biologics are as safe as the original products, and that we provide the necessary knowledge to medical practitioners in the use of these products.

As we study potential competition models, should we be guided by a one size fits all approach or should we allow different approaches, and, if so, when, how, and what discretion should we give FDA to use those, or should there be a variation from one product to another? What study should support follow-on biological applications? Can a generic biologic product be created that is genuinely or sufficiently interchangeable? People tell us yes, people tell us no. But in this area of enormous complexity, I am not convinced that we can give a decent answer to that question. I am convinced that all these questions could be answered and that there is a way forward in developing sound follow-on biologic policy that provides greater access to current products and supports innovation in developing new ones.

I look forward to contributing to that discussion, and I know that this committee is fully up to the task for which we were created,

and that is dealing with questions of this kind. I am pleased this hearing is being held. I look forward to the testimony, and I anticipate much needed feedback from our members. And I thank you, Mr. Chairman.

Mr. PALLONE. Thank you, Chairman Dingell. The gentlewoman from Tennessee, Ms. Blackburn.

OPENING STATEMENT OF HON. MARSHA BLACKBURN, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF TENNESSEE

Ms. BLACKBURN. Thank you, Mr. Chairman, and I want to say welcome to our witnesses today. Members on this committee have heard me talk a little bit about serving in the State Senate in Tennessee, and one of the things that I worked very diligently on while I was there was starting our Tennessee Biotech Association. And now that has 130 members across our state, and they really have become the recognized authority on biotech research in our state. Right now we have got about 300 companies that are life science companies that are working in Tennessee that are innovating every day, and they are working with pharmaceutical companies and bio-science companies large and small to create new products and therapies and protocols. And we are very pleased with the work that they are doing.

We are also pleased with the work that is being done by many of our universities in Tennessee, which have taken a lead in this. And they received \$580 million in external funding for biotech related research in our universities in the past year, and the University of Tennessee Health Science Center has Memphis Bioworks. We have complimentary work that is being done at St. Jude's. We have the life sciences center where Vanderbilt has a partnership and that is in the mid state area East Tennessee State University of Tennessee and Oak Ridge over on the east side of our state, and in the past 6 years along with the funding that has gone to the universities you have seen just under \$1 billion in venture capital go into innovations.

So I am pleased to be able to praise that innovative industry in our state but I will tell you I am very concerned about protecting the intellectual property of the industry in that state, and, quite honestly, as I read through your report, it was something that was of concern to me. And I am going to have some questions for you today as we move forward with this hearing. One of the things that I felt as I read your report, if you followed the scenario, the patient scenario that you lay forth, then it appears that bio-similars could be brought to market while they are still infringing on valid patents. And as my colleagues know, last week when we debated the energy bill, I sought to bring intellectual property protection for those innovators that are working in the energy sector. Yesterday on the floor, Congressman Larson, Congressman Kirk and I had an amendment that went in to provide protection for this innovation.

So this raises some red flags with me of how infringement could be allowed and product brought to market. It raises red flags to me that it is uncertainty that would be placed on our innovators. And I see that as a hamper to R&D which we badly need. I know I am

over my time, and we are going to have votes. I will yield back, and I do look forward to the questions. Thank you, Mr. Chairman.

Mr. PALLONE. Thank you. The gentleman from Utah, Mr. Matheson.

**OPENING STATEMENT OF HON. JIM MATHESON, A
REPRESENTATIVE IN CONGRESS FROM THE STATE OF UTAH**

Mr. MATHESON. Thank you, Mr. Chairman. I think we all know as we go into the 21st century and we look at the U.S. economy innovation is such a key factor in how our economy is going to succeed. I think it is very important to remember that in the context of today's hearing because within the innovation economy few industries have more promise and more uncertainty and risk than the biotechnology industry. The biotech industry supports more than 3.2 million jobs in the United States, and we all know many of these are high wage jobs, but we should also acknowledge that this is an industry where the U.S. is still the leader in the world. This is one of those centers of excellence that is in the United States when you look at the global economy.

Yet with all that good news more than 80 percent of the biotech companies in our country remain unprofitable, and a third of the companies had less than 6 months cash on hand. And this is with no competition from follow-on products. The companies that make up the majority of this industry are small. They have no source of revenue and they are operating solely on the hope that they will achieve a major breakthrough in medicine. So one of the main issues up for discussion today is the issue of date of exclusivity, how much time should an innovative biotechnology product have on the market to try to recoup investment in research and development before a follow-on biologic is approved. The average cost of developing a biologic is about \$1.2 billion.

Clearly, that is an expensive investment, particularly when you have no revenues coming in the door. I think we all can agree that competition in the market for medicines is a good thing. It brings down costs for individuals and for the health care system as a whole, and I fully support establishing a pathway for approval of follow-on biologics. However, I believe we need to be sure we are creating appropriate incentives for biotechnology companies to take the risks involved in bringing these medicines to patients. Now I understand that the FTC believes that 5 years is a sufficient period for data exclusivity for innovative biotechnology products. I disagree.

As I said earlier, this is one of America's strengths, but we got to look at the context of global competition. The exclusivity period in Europe is longer than 5 years. This is an industry that can move offshore in a moment, and as members of Congress, we need to take that in consideration when we set this type of policy. A recent report from Duke University shows that the break even point for most biologics is somewhere between 12 and 16 years. With an appropriate incentive, the researchers at Duke believe a few companies or venture capitalists will invest the necessary capital to research and develop a biotech product.

These products are going to be developed in this country, not necessarily with taxpayer dollars. That last statement I just made

about this is an industry that is financed through venture capital and other private capital markets, and the public policy platform we will establish proper incentives, I hope, to allow that private investment to happen. These are the issues we ought to be talking about today. It is our job to take these steps to make sure this innovation agenda has an opportunity to succeed in this country. And I would hope, Mr. Chairman, as others have voiced that this subcommittee can bring in other witnesses besides just the one panel today to bring in other points of view as we examine this very important issue. I look forward to working with the committee on that, and I will yield back the balance of my time.

Mr. PALLONE. Thank you. The gentleman from Georgia, Mr. Gingrey.

OPENING STATEMENT OF HON. PHIL GINGREY, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF GEORGIA

Mr. GINGREY. Mr. Chairman, thank you very much. I would tend to agree with Ms. Eshoo that getting the report from the FTC at 2:00 yesterday afternoon really allows very little time to go through the 120 pages. I have to admit that I haven't had an opportunity to go through any of it, so I certainly do look forward to the witness that we are going to hear from shortly. This is a hugely important issue, this issue of follow-on biologics, and as we all know there are 2 bills introduced on the one hand by leadership on the majority side combined with some leadership from the minority side, and also a bill on the minority side co-authored by Ranking Member Barton. I looked at these bills. I have studied them. I have tried to understand on the one hand 16 years, I guess, of exclusivity and on the other hand 8 years. The issue of interchangeability, once these generic biologics, follow-on biologics, are actually approved by the FDA, I think is a very important issue.

And it is tough. It is a tough thing to decide on, and we just need, as my colleagues have said, as much information as we can possibly get, particularly in regard to patient safety because as the chairman emeritus said these are not single molecules or small molecules as we dealt with back in 1984 under Hatch-Waxman. These are different. These are living cells, and every manufacturing process for these drugs are different, and there is no way to make them completely the same, so it is going to be a tough thing. I would hope that maybe there is room for compromise, quite honestly. As we listen to the debate and study further the 2 particular bills because there are great members that are trying to do the right thing and trying to make sure that we get cost effective, I don't want to say cheap, but cost effective, the very expensive medications to the public as soon as possible, but also that we have to always keep in mind safety. So I look forward, Mr. Chairman, to the hearing and getting more information on this hugely important issue. And yield back.

Mr. PALLONE. Thank you. The gentlewoman from California, Ms. Harman.

OPENING STATEMENT OF HON. JANE HARMAN, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF CALIFORNIA

Ms. HARMAN. Thank you, Mr. Chairman. I am a new member to this subcommittee, and I surely agree with Ms. Eshoo that this subject is complex, and I am persuaded that I don't know enough about it to have a final opinion. That is why I am happy we are having this hearing, and that we will have a series of hearings in the fall. I have not co-sponsored either of the pending bills because I feel I need to learn more. But surely I know enough to believe that we should be getting reports more than 18 hours in advance of hearings, and I hope that in the future that will happen so that all of us can be as knowledgeable as possible. I just want to say a couple things about the general subject.

First of all, although new to the committee, I am not new to this earth and I am not new to Congress, and I remember 1984 when Henry Waxman did something very impressive, and that was to strike an agreement with his political opposite Orin Hatch on a bill that the drug industry strongly opposed and that has led to considerable progress, so I really think these things can happen and be done right, and that is a history in our committee, and hopefully we will follow it again. But this time, I think this subject is more complicated and I think the implications, as Mr. Matheson said, for the future of the U.S. industry are grave. I don't know much about this subject, but I do know what we did to the U.S. commercial satellite industry when in my opinion we got it wrong in the late 1990's, and we basically took away the market edge for our U.S. satellite makers.

Now we are trying to get it back. Hopefully we will, but we lost 10 years, and so I just want to make sure we get this right, and I want to be sure that I make the best contribution I can as a hopefully thoughtful member of this committee. So I thank you for holding this hearing, and I look forward to learning a lot more about this subject. I yield back.

Mr. PALLONE. Thank you. The gentleman from Pennsylvania, Mr. Pitts.

OPENING STATEMENT OF HON. JOSEPH R. PITTS, A REPRESENTATIVE IN CONGRESS FROM THE COMMONWEALTH OF PENNSYLVANIA

Mr. PITTS. Thank you, Mr. Chairman. I would like to thank you for convening this hearing on the Federal Trade Commission's report, Emerging Health Care Issues: Follow-on Biologic Drug Competition. I think all of us realize the potential of follow-on biologics, and I believe we all agree on the need to set up a pathway sooner rather than later. I must say also that it would have been more helpful to give the members a little more time until we had a time to read and analyze this 120-page report, which was released just yesterday before having the hearing. I am quite concerned by the report's assertion that no period of data exclusivity is necessary for pioneer or brand biologics because patents and market pricing should provide sufficient protection and incentive. This logic has worked well for small molecule drugs governed by Hatch-Waxman but as this report points out multiple times there are significant differences between small molecule drugs and biologics.

As the report acknowledges, a generic small molecule drug is identical to its brand counterpart. A follow-on can only be similar to the brand biologic. It is this space between identical and similar that opens the door for a follow-on to circumvent or skirt one or more of the brand biologic's patents. With this uncertainty over whether a patent will actually protect the brand biologics investment biotech companies and the venture capitalists that fund them may reassess the cost and risk involved in the development of new biologics and opt not to go forward with new drug development. Stifling innovation and potentially impeding patients' access to the most promising, cutting edge biologics is surely not the goal of anyone on this subcommittee.

Data exclusivity provides the certainty brand biologics need to spend hundreds of millions of dollars and years investing in the research, development, and approval of new drugs, and the assurance that this investment can be recouped. I would ask our witnesses to carefully explain why they believe that patent circumvention by bio-similar companies is not a valid scenario. Thank you, and I yield back the balance of my time.

Mr. PALLONE. Thank you, Mr. Pitts. The gentlewoman from the Virgin Islands, Mrs. Christensen.

OPENING STATEMENT OF HON. DONNA M. CHRISTENSEN, A REPRESENTATIVE IN CONGRESS FROM THE VIRGIN ISLANDS

Mrs. CHRISTENSEN. Thank you, Mr. Chairman, and thank you for beginning this discussion on this very important and complex issue at this hearing. As I understand it, the report was requested basically to determine if follow-on biologics would result in reductions in cost of these complex but very important therapeutic drugs, and anyone who knows me would know that one of my concerns is that life improving or saving medication be accessible to everyone, and, yes, cost is an important barrier to that. But as a physician, safety trumps everything. I have seen substandard meds marketed in the Caribbean, and in small molecular drugs that may not be a dangerous difference. The situation with bio-similars or follow-up biologics is totally different. I only had a chance to read the executive summary and some of the first pages of the report, but what I have taken away so far is a clear understanding that biologics are very complex, large molecules produced under very sensitive conditions that are not easy to reproduce exactly, that significant investment is made in their production and that if reduction of cost is what has generated the request for this report FOBs are not likely to result in much of a price decrease.

If the latter is true then why sacrifice safety? And some questions remain unanswered. Why accept a similar rather than the same in the case of such a complex medication when a tiny difference could make a difference in its action and its immunogenicity. I am puzzled by the assertion also that a shortened patent life will not stifle innovation. If it takes 12 to 14 years to recoup investment as demonstrated by a peer review article by Duke Professor Grabowski, and that is likely after many trials have failed at that company and they have experienced financial losses, why should these complex molecules not have a longer time? Very importantly, the report states that technology is not yet, and I am

quoting here, “technology is not yet robust enough to determine whether an FOP product is interchangeable with the pioneer product.”

That statement, plus the fact that not a single country in the EU has authorized interchangeability, and several have outlawed it, should slow down any rush to allow products that are only similar to the pioneer, and to require more of any follow-on manufacturer to prove safety. It seems to me that sufficient uncertainty exists so that the FTC didn’t even make a specific recommendation for a period of exclusivity. I would like to see these important drugs reach everyone, and that means exploring ways to ensure that that happens, including having the pharmaceuticals look after a period of time perhaps reducing the costs, but I am convinced that shortening the time of patent and data exclusivity would adversely impact needed innovation, and it seems to me that based on the complexity of the large molecules and the lack of information on several factors, we should err on the side of safety and make sure that we do no harm. So I welcome Commissioner Harbour and look forward to your testimony. Thank you, Mr. Chairman.

Mr. PALLONE. Thank you. The gentleman from Indiana, Mr. Buyer.

OPENING STATEMENT OF HON. STEVE BUYER, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF INDIANA

Mr. BUYER. I have come here today, I also like my colleague, Jane Harman, I have not co-sponsored either of these 2 bills yet, and I find myself in a curious position why we are even seeking the counsel of the Federal Trade Commission on an issue whereby we are most concerned with regard to the drug safety and efficacy. When I look at the commissioners from the Federal Trade Commission, none of them have any experience in public health whatsoever. We got lawyers. Well, I am a lawyer too, so what I need is not the advice or counsel of another lawyer. I need advice and counsel from public health, from scientists. So we have a conversation today lawyer to lawyer. You can give me your opinion on what you think the marketplace is and what it is like, and I guess if you are going to tell me about trying to promote competition in the drug industry, big versus small, and how we protect innovation as part of your core mission of the FTC, I guess we may as well ask you to report on NASA.

Gee, let us talk about what big company it out there and how we can promote innovation to do exploration in space. Hey, the last frontier isn’t even space, it is marine. So maybe we should ask for a report from the FTC about the exploration on the ocean floor. You can give me an opinion on that. Maybe I should ask for—I will just make it up. So I am sitting here today as a curious member of Congress that I have come here to listen to lawyers tell us what they think about drug efficacy and safety. Now I haven’t had a chance to read this. I am more than anxious to look at it. I am also curious as to who initiated this. Did anyone from Congress ask you to do this? I don’t know. So I am interested for you to let us know why you initiated this, why this group of lawyers think that your opinion is so important with regard to efficacy and the safety of drugs.

Now what bothers me the most is that what I have learned over the years in dealing with the drug industry and biologics is that we do everything we can to promote this innovation, yet we try to find science in narrow populations, and it is very challenging because when you go into the marketplace, how do you raise that at risk capital, and if we don't give these companies an opportunity to recoup their cost and make a profit, they won't go into narrow spectrums, and if they won't go into narrow spectrums then people then turn to government and say that government, you have to do it. And if it is all about innovation, safety, and efficacy, I want to hear from the experts, Mr. Chairman. So what I am hopeful is that if you are going to do this today, please bring us a panel of experts, the FDA, bring in the scientists so that we can have equal quality here with regard to substantive testimony. That is what I am looking for. That would be my request of you, Mr. Chairman. I yield back.

Mr. PALLONE. The gentleman from Texas, Mr. Green.

**OPENING STATEMENT OF HON. GENE GREEN, A
REPRESENTATIVE IN CONGRESS FROM THE STATE OF TEXAS**

Mr. GREEN. Thank you, Mr. Chairman, and like my colleagues, I have concerns about this hearing on the FTC's report that we received yesterday on follow-on biologics competition. We have heard this will be the only hearing on the issue of follow-on biologics because the schedule will not accommodate additional hearings on the topic. If we are going to have a fair debate on follow-on biologics and the issues surrounding H.R. 1548, the Eshoo-Barton-Inslee Pathway to Bio-Similars Act, which I am a co-sponsor, and H.R. 1427, the Waxman-Pallone-Deal Promoting Innovation and Access to Life-Saving Medicine Act, the arena for those should not be centered around a hearing with one witness from the FTC.

Follow-on biologics are extremely complex issues and members of this committee are divided between the 2 bills pending before us. One hearing with one witness who isn't from the FDA, an innovator company, a generic drug company, or even a patient who has used biologics is not a true hearing on the difficult issues surrounding follow-on biologics. We believe we need to have a hearing with at least the FDA before this committee moves forward with any legislation on follow-on biologics. I think we can all agree that there needs to be a regulatory path in this country to follow-on biologics, and however we resolve the differences between the 2 bills, we need to consider the implications for employers, innovators, the generic industry, and, most importantly, the patients who depend on these life improving and life-saving therapies.

Biologics offer tremendous promise in the treatment of disease but there is no question we have to get it right. The undeniable fact is biologics are different from the small molecule drugs and present unique concerns about their safety and effectiveness. Holding one hearing that doesn't allow us to explore the questions such as what effect does a small change in immunoacid sequence produce, is that effect large enough and concerning enough to warrant additional clinical trials before the follow-on biologics is available to the public, can we in good conscience consider the follow-

on product safe if they are never even tested on the human population?

I share the goal of lowering patients' costs to follow-on pathway but not at the expense of the same patients' safety. Any action by the committee must balance the desire for the lower cost of biologics with the need to preserve the incentives for innovation and patient safety so that more Americans can benefit from the therapeutic promise of biologics. And again I thank you and yield back my time.

Mr. PALLONE. Thank you. The gentleman from Illinois, Mr. Shimkus.

OPENING STATEMENT OF HON. JOHN SHIMKUS, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF ILLINOIS

Mr. SHIMKUS. I knew I could be here when the gavel dropped and go to the next meeting and still make it, so I apologize to the Commissioner. I would just read from the report here on the executive summary. Current technology does not yet allow the creation of an exact replica of a pioneer biological drug product according to the FDA. In addition, technology is not yet robust enough to determine whether the follow-on biologic product is interchangeable with the pioneer products such that a patient would be able to switch between the 2 products without risk of an adverse effect. Follow-on biologics are not chemical compounds. We need more hearings on this, Mr. Chairman, and we need to have science brought in. And with all respect to the FTC, they are not the ones. They are not the ones to give us the direction on the safety and efficacy on follow-on biologics, so I look forward to that, and I hope we can follow up with more hearings. I yield back.

Mr. PALLONE. Thank you. The gentlewoman from Wisconsin, Ms. Baldwin.

OPENING STATEMENT OF HON. TAMMY BALDWIN, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF WISCONSIN

Ms. BALDWIN. Thank you, Mr. Chairman. And thank you, Commissioner Harbour, for joining us today. I have really been interested in the issue of follow-on biologics for a number of years. I happen to represent a district that is rich in intellectual capital in this area. The University of Wisconsin-Madison has produced some of the world's leading research in biologic drugs. We also have a unique entity in my district called the Wisconsin Alumni Research Foundation. We call it WARF. And what they do is they work with business and industry to transform university research into real products benefitting society at large. It was founded in 1925 to manage the University of Wisconsin-Madison discovery that eventually eliminated the childhood disease rickets, and today WARF holds nearly 100 patents related specifically to biologics.

I am certainly supportive of the creation of a pathway for the approval of bio-similars, and we will hear from the FTC this morning that when we do create this pathway current patent protections coupled with market-based pricing are sufficient to continue to spur innovation in the biologic drug market. And yet on the ground I hear often times the opposite is true. Even if with current patent

protections and without a pathway for bio-similars, WARF is having trouble finding companies to buy and license those 100 plus biologic patents that I referred to and that they currently hold. Developing biologic drugs is a billion dollar enterprise with an extraordinarily high failure rate. To take that on knowing that another company could invest a fraction of that amount and take even a small portion of your market share may be enough to rethink the enterprise altogether.

I am extraordinarily proud of the companies in my district who have taken on this risk in hopes of saving lives and improving health. Just one example is the example of Flugen located in Madison. They are working on developing influenza vaccines, and we know that this is a timely and critically important enterprise. Flugen, like the vast majority of biotech industry colleagues, is a very small company. It does not have the profit margins of 50 and 60 percent, yet these are the profit margins that are used to conduct these economic analyses that conclude that only minimal data exclusivity is necessary. Without sufficient data exclusivity protection Flugen faces the risk that a company will really come in and take a free ride off of their clinical data and design around their patent forcing them out of the market entirely.

One final point, Mr. Chairman. The FTC report seems to conclude that a long period of data exclusivity would hamper innovation. Currently, with no pathway biologics enjoy infinite data exclusivity and yet we have had an astounding innovation in this arena. So you really only need to look to the second congressional district in Wisconsin to see the best proof of that. Thank you, Mr. Chairman, and I yield back my balance of time.

Mr. PALLONE. Thank you. The gentlewoman from North Carolina, Ms. Myrick.

Ms. MYRICK. Thank you, Mr. Chairman, but I will waive.

Mr. PALLONE. The gentleman from Pennsylvania, Mr. Murphy.

OPENING STATEMENT OF HON. TIM MURPHY, A REPRESENTATIVE IN CONGRESS FROM THE COMMONWEALTH OF PENNSYLVANIA

Mr. MURPHY OF PENNSYLVANIA. Thank you, Mr. Chairman. Part of what we have to do here with Solomon's sword is to understand that drugs that are not affordable offer little consolation, and a drug that is not invented offers little cure. A couple years ago when we had a hearing on this issue of follow-on biologics, I talked about a constituent of mine who had pancreatic cancer, and he at that time was taking experimental biologic drug which actually shrank his tumors down considerably, but unfortunately ended up with some kidney failure and he died in the process. It was exciting to watch how his cancer was going away and otherwise would be a lethal problem for him. It was troubling to see how he had to jump through a lot of hoops to get the treatments.

But, moreover, I want to make sure that we are continuing to do everything we can to encourage companies to make the investments to come up with these cures. I know that part of what we are facing here is a way that once we come up with these cures, how do we make sure that people can afford these drugs, and that is what I hope we have a lot of discussions on, a lot of hearings

to really work out some mechanism whereby these become affordable. But again I say that if the drug is not invented, there is no cure, and, therefore, no hope. And I hope that as we proceed with this, we will both hear from witnesses with some ideas along these lines, but also continue to deliberate among ourselves in using all that is possible to make sure that we do not stop either end of this. And with that, I yield back.

Mr. PALLONE. Thank you. The gentleman from Ohio, Mr. Space.

**OPENING STATEMENT OF HON. ZACHARY T. SPACE, A
REPRESENTATIVE IN CONGRESS FROM THE STATE OF OHIO**

Mr. SPACE. Thank you, Mr. Chairman, for the opportunity to provide my perspective on what is clearly a very difficult and somewhat controversial issue. In listening to the opening statements of my colleagues on both sides of the aisle, it is clear that we are arriving at a consensus, and as very eloquently stated by Mr. Murphy from Pennsylvania, the need to innovate is directly conflicting right now with the need to provide affordable biologic medication. We have seen a tremendous boom in the manufacture of biotechnology and industry. Generally, the United States has been a leader, and it is something that we can be very proud of. I am sincerely torn right now on this issue because I have a child who suffers from a disease who is alive today because of biologics, and I understand the need to foster innovation to create an environment in which those biotech companies that are flourishing in this country right now are able to take the risks necessary to innovate and create new treatments and cures.

At the same time, I come from a district where many people don't have quality health care. Many people do not have the ability to pay considerable sums for these sophisticated medicines. And I do take hope in listening to the opening statements of my colleagues on both sides of the aisle that this committee will face this challenge in a way that it should with a sincere and passionate desire to do the right thing. I look forward to working with you, Mr. Chairman. I appreciate the hard work that you have devoted to this issue. And I do look forward to hearing the testimony today, and I yield back. Thank you.

Mr. PALLONE. Thank you. The gentleman from Georgia, Mr. Barrow.

Mr. BARROW. I waive.

Mr. PALLONE. The gentlewoman from Ohio, Ms. Sutton.

**OPENING STATEMENT OF HON. BETTY SUTTON, A
REPRESENTATIVE IN CONGRESS FROM THE STATE OF OHIO**

Ms. SUTTON. Thank you, Mr. Chairman for holding this extremely important hearing, and I look forward to hearing what the panelists have to say. In the United States, competition has always been an engine for innovation, and that has been true in the health care and the industry that supports it. And while national unemployment numbers continue to be a source of concern the Bureau of Labor Statistics reported that in May of this year health care employment increased by 24,000. This increase is in line with the average monthly job growth so far in 2009. Clearly, when it comes to the need for health care, demand far outweighs supply and it is

important to nurture the technology and advancement that leads to medical breakthroughs. However, in doing so, we must also consider that those who use our health care system, we have to be accountable to them as well.

Patient access to life-saving technology and drugs is critically important with the cost of health care bankrupting American families. We must consider how we can make things work for our citizens. It is important that we have a pathway for options such as biologics, but it is equally important that this pathway be safe. Our experience in the field of generics has taught us that multiple entrants into a pharmaceutical field or category can drastically drive down price and increase accessibility of drugs for patients.

And I am eager to hear from our panelists about how the FTC envisions the market for follow-on biologics that will allow innovation to flourish, and also serve to better our health care system and protect the health and the wallet of Americans. I yield back.

Mr. PALLONE. Thank you. The gentleman from Iowa, Mr. Braley.

**OPENING STATEMENT OF HON. BRUCE L. BRALEY, A
REPRESENTATIVE IN CONGRESS FROM THE STATE OF IOWA**

Mr. BRALEY. Thank you, Mr. Chairman. If you have been paying attention to what my colleagues have been saying this morning, you will appreciate this is a tough job. This is a tough job that we have. I have friends on both sides of this issue. You hear great arguments on the strengths and weaknesses of these various proposals, and I think the thing that unites us all is a strong desire to make something happen that is going to benefit the people who are going to realize whatever potential medical gains there are to be realized from the research and development of biologics, and that is what brings us here and motivates us. I want to thank the chairman for holding this important hearing. And we all know that establishing a fair pathway for follow-on biologics is extremely important, and we stand to see tremendous health care improvements as biologics continue to come to the market.

And when you look at the challenges we are facing with the broader health care reform debate these are questions that have enormous implications going forward, and that is why we are all so focused on this issue. We know that biologics have improved the treatment of many Americans and save countless lives, and these innovations will only see more and more use in coming years. The proteins that form the bases of biologics are extremely complex, and I must say the policy questions surrounding the creation of a pathway to the market are almost just as complex. Any pathway for follow-on biologics must ensure fair competition without discouraging innovation in the industry.

We owe many of our biggest medical achievements to those who have spent significant time and resources researching and experimenting with drugs, and biologics is no different. We need to continue innovating and we must make sure that every American who needs them can access life-saving drugs and biologics that are a result of that innovation. I have been studying this issue closely since joining this committee and hearing from parties on all sides of the issue. I am glad to see that we are gearing up to address the issue today, and I am confident at the end of the day we will have a pro-

posal that both encourages innovation and ensures affordable access to those life-saving biologics.

I look forward to continuing in these negotiations to make sure that Iowans that I represent continue to benefit from innovative, affordable medications. The FTC has a great deal of expertise and a long record of ensuring fair competition in the marketplace, but that record is sometimes not always perfect. They have thoroughly examined Waxman-Hatch in the past, and I always take their findings very seriously. That is why I look forward to today's testimony, to the follow-up hearings we are going to have, and I want to thank the chairman for convening the hearing.

Mr. PALLONE. Thank you, Mr. Braley. The gentleman from Maryland, Mr. Sarbanes.

Mr. SARBANES. Thank you, Mr. Chairman. I don't have much to add to what has been said. Obviously, we have on one end of the equation the need for research and development to proceed in a way that is meaningful and leads us to new discoveries that can benefit consumers. On the other hand of the equation, we have got the interest of affordability and access for the consumer. And we are struggling, or we are not struggling yet, we are working hard to figure out where the right balance is going to be. The testimony today is obviously going to be helpful in that process. I just hope that when we reach the balance, we come to it principally through the perspective of what makes sense for the consumer. And so I look forward to the testimony, and I yield back my time.

Mr. PALLONE. Thank you. The gentlewoman from Illinois, Ms. Schakowsky.

OPENING STATEMENT OF HON. JANICE D. SCHAKOWSKY, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF ILLINOIS

Ms. SCHAKOWSKY. Thank you, Mr. Chairman. As we continue moving forward on health reform legislation, it is important that we take a long, hard look at prescription drugs and how we can work together to reduce drug prices and increase patient access to life-saving drug therapies. I am a co-sponsor of H.R. 1427, and I thank Chairman Waxman and Chairman Pallone for sponsoring this legislation because I believe this bill effectively safeguards against unsafe drugs entering the market while allowing patients to access lower cost generic drugs. I recognize the importance of encouraging innovation in the pharmaceutical industry. As the report authored by the FTC shows, innovation will not be hampered by allowing biologic generics into the market.

First, the research shows that it will most likely take 8 to 10 years to develop the manufacturing capacity to make a similar and interchangeable generic for a brand name biologic. More importantly, the amount of money required to produce the generic between \$100 million and \$200 million will limit the number of generic manufacturers. In other words, assuring that generic manufacturers can enter the market after a 5-year exclusivity period will pose little threat to the brand name industry but it would have enormous pay backs for consumers. I strongly believe that encouraging competition particularly in the health care industry not only

promotes creativity and energizes researchers to discover better and more effective products but it reduces costs.

I think it is important that we give this complex issue some context. Like many of the states represented on this committee, Illinois is facing a budget crisis, a deficit that is approaching \$11 billion. As a result, many of the programs currently in place to help our citizens are facing drastic cuts. Among those programs headed for a cut includes the Illinois Cares RX program, a program that provides prescription drug assistance to 172,000 seniors with high drug costs. Many of these drugs cost patients tens of thousands of dollars each year. Some can be over \$100,000, and out-of-pocket copayments could run \$10,000 to \$20,000 a year. We obviously have to do all we can to bring down drug costs for patients.

I believe that H.R. 1427 will help us do that. Mr. Chairman, I look forward to working with you and further the health and well-being of our constituents and bring drugs to the market in a safe and timely and affordable way. I yield back.

Mr. PALLONE. Thank you. The gentlewoman from Colorado, Ms. DeGette.

Ms. DEGETTE. Mr. Chairman, I will submit my statement for the record. Let me just say an issue that none of us knew one thing about, we now are quite conversant, and I think we need to move forward and talk about how we are going to resolve it. I am very much eager to hear the testimony of Commissioner Harbour today. I think that will lend some light onto this very tough decision we have to make. And with that, I will yield back.

Mr. PALLONE. Thank you. I think we have heard all the opening statements. I just want to make sure that is true. Yes. OK. We will now turn to our witness, and thank you for being here. First, let me say our witness, actually we only have one witness, is the Honorable Pamela Jones Harbour, who is the commissioner from the Federal Trade Commission. However, my understanding is she has been joined by Mr. Wroblewski, who is the prime author of the report. And he is not going to testify, but will be available for questions is the way I understand it. And we know we have 5-minute opening statements, and then we may get back to you later with additional written questions as well, but we will have questions from all the panelists, from all the members of the subcommittee today. So if you would begin, thank you.

STATEMENT OF PAMELA JONES HARBOUR, COMMISSIONER, FEDERAL TRADE COMMISSION

Ms. HARBOUR. Thank you, Chairman Pallone, Ranking Member Deal, and members of the subcommittee. I am Pamela Jones Harbour, a Commissioner of the Federal Trade Commission. I am joined by Michael Wroblewski, Deputy Director of the FTC's Office of Policy Planning. Thank you for inviting us to testify here today. I appreciate this opportunity to provide an overview of the Commission's recently released report called Emerging Health Care Issues: Follow-On Biologic Drug Competition. A primary goal of our report is to examine how competition is likely to evolve in biologics market in particular between pioneer biologics and follow-on biologics or FOBs. The report sets forth our findings regarding the

competitive dynamics of FOBs, and we hope that our recommendations will inform the legislative debate.

I note that the report does not address any specific bills. The Commission recognizes that legislators are balancing many different objectives, as they seek to craft a solution that best protects the public interest. The Commission has limited its recommendations to competition issues, which are our core area of expertise. We believe, of course, that this competition perspective is of critical importance in the FOB debate, which is why we are grateful to have been given, literally, a seat at the table today.

If Congress can create a balanced pathway for FOBs, and also pass legislation to eliminate pay-for-delay patent settlements between branded and generic companies in small molecule markets, then Congress will have taken substantial steps to ensure that all Americans have access to affordable life-saving medicines. On behalf of Chairman Leibowitz, I commend the Commerce Committee for moving legislation to ban these patent settlements through the Consumer Protection Subcommittee last week. The report's basic premise is that competition between pioneer biologics and FOBs is likely to look much more like current competition between 2 or more branded drugs that treat the same medical condition, for example, Enbrel and Remicade, which both treat rheumatoid arthritis. It will look less like current competition between branded and generic versions of a drug and I will explain why the Commission reached this conclusion, and I will also identify some implications for legislation seeking to create an abbreviated regulatory approval pathway for FOBs.

But first, I will begin by highlighting some important characteristics of the biologics marketplace. As you know, the emergence of biologic drugs has dramatically improved the lives of thousands of Americans over the past few decades. For example, the biologic Herceptin is used to treat breast cancer, and an annual course of treatment costs about \$48,000 a year. One way to reduce the costs of biologics would be to authorize the Food and Drug Administration to permit follow-on biologics to enter the market once a biologic drug's patents expire. However, there is no statutory or regulatory pathway to allow abbreviated FOB entry without the FOB applicant having to duplicate existing knowledge about safety and efficacy. This duplication represents an inefficient use of limited R&D resources. Also, as the FDA has explained, repeating all of the clinical trials raises ethical concerns associated with unnecessary human testing.

Elements of the Hatch-Waxman Act provide a model for reducing FOB entry costs and addressing ethical concerns. Hatch-Waxman does not require generic applicants to duplicate the clinical testing of branded drugs that have already been proven safe and effective. Hatch-Waxman has successfully reduced drug prices, has broadened access, and has hastened the pace of innovation. And if pay-for-delay settlements are prohibited, these benefits of Hatch-Waxman will be preserved. But as the report describes, according to the FDA, there are key scientific differences between biologic and small molecule drug products. Most notably, under Hatch-Waxman, the generic applicant must show that the product is bio equivalent to

the branded drug product. This is important because it means that the product is identical.

In stark contrast, according to the FDA, biologic products cannot be perfectly duplicated, at least not based on current science. Technology is not yet robust enough to determine whether an FOB product is interchangeable with the pioneer product. Current FOB legislative proposals reflect the complexities of biologics. They would permit FDA approval of an FOB drug that is similar to, but not an exact replica of the pioneer biologic product. Under these proposals, the FDA could rely on its previous findings regarding the pioneer biologic drug's safety and efficacy to the extent those findings would also be relevant to the FOB. An FOB manufacturer likely would save on some clinical testing expenses, which would reduce entry costs.

So with that background in mind, let me turn to the Commission's report. The purpose of our study was to evaluate how FOB competition is likely to develop and evolve, paying particularly close attention to the differences between small molecule and biologic drugs. The study was coordinated by an interdisciplinary FTC team, headed by Mr. Wroblewski, that included not only pharmaceutical industry experts, but also patent lawyers and economists. As part of its inquiry, the Commission solicited 2 rounds of public comments which attracted submissions from approximately 30 industry participants and other stakeholders.

In November 2008, the Commission conducted a public roundtable discussion that included over 30 panelists. The Commission also has examined European markets where FOB entry has occurred. In the interest of time, let me briefly summarize the 4 major reasons why FOB competition is not likely to be like generic brand competition. First, it is the extraordinary cost and time necessary to develop an FOB, which will sharply limit the number of competitors who can afford to enter, and also will limit the discounts the FOB can offer in relation to the pioneer price. Second, follow-on entry will not radically erode the pioneer's market share. Third, the specialty pharmaceutical characteristics of FOBs are likely to further constrain the FOB entrant's ability to gain market share. And the fourth reason is because biologics are provided in clinic-type settings as part of medical treatments. They are not purchased and reimbursed in the same manner as small molecule drugs.

As a result of all of these factors, the Commission's report predicts that FOB markets are likely to develop with the following characteristics. First, that FOB entry is likely to occur in biologic drug markets with more than \$250 million in annual sales. Only 2 or 3 FOB manufacturers are likely to attempt entry in competition with a particular pioneer drug product. These FOB entrants likely will not offer price discounts larger than 10 percent to 30 percent of the pioneer product's price. Although this discount is not as steep as with small molecule generic drugs, it does represent millions of dollars in consumer savings for these very expensive products.

Pioneer manufacturers are expected to respond by offering competitive discounts to maintain their market share. This price competition likely will increase consumer access and further expand

the market. Without automatic substitution, FOB market share acquisition will be slowed. Pioneer manufacturers likely will retain 70 percent to 90 percent of their market share. This means that a pioneer firm will continue to reap substantial profits for years, even after entry by an FOP. FOB market dynamics will contrast sharply with the market dynamics of generic drug competition, where lower-cost generic entry plus automatic substitution lead to rapid erosion of the branded drug's market share. When the first generic drug enters the market, it generally offers a 25 percent discount off the branded drug's price. As additional generic firms enter, and often there are 8 or more of them, the price discounts reach as high as 80 percent.

Given these likely dynamics of FOB markets, the Commission next asked whether any additional——

Mr. PALLONE. Commissioner, I am sorry, but you are like twice the time so far so——

Ms. HARBOUR. OK. Then I will stop.

Mr. PALLONE. No, no. Just wrap up. I don't want to stop you completely. Just try to summarize the rest, if you could.

Ms. HARBOUR. I would say that the findings have several implications for the design of an abbreviated approval system. I think first pioneer manufacturers are unlikely to need additional incentives to continue to innovate in the face of FOB entry beyond the existing patent protection and market-based pricing. I would be ready to answer questions now. We can engage in a Q and A, and I know that the committee is very interested to hear what we have to say, so thank you.

[The prepared statement of Ms. Harbour follows:]

Oral Statement of Commissioner Pamela Jones Harbour

Before the
Subcommittee on Health
Committee on Energy and Commerce
United States House of Representatives
June 11, 2009

"Emerging Health Care Issues: Follow-on Biologic Drug Competition"

Introduction

Chairman Pallone, Ranking Member Deal, and members of the Subcommittee, I am Pamela Jones Harbour, a Commissioner of the Federal Trade Commission. I am joined by Michael Wroblewski, Deputy Director of FTC's Office of Policy Planning. Thank you for inviting us to testify today.

I appreciate this opportunity to provide an overview of the Commission's recently released report, *"Emerging Health Care Issues: Follow-On Biologic Drug Competition."* A primary goal of our report is to examine how competition is likely to evolve in biologics markets – in particular, between pioneer biologics and follow-on biologics, or FOBs. The report sets forth our findings regarding the competitive dynamics of FOBs, and we hope that our recommendations will inform the legislative debate.

I note that the report does not address any specific bills. The Commission recognizes that legislators are balancing many different objectives, as they seek to craft a solution that best protects the public interest. The Commission has limited its recommendations to competition issues, which are our core area of expertise. We believe, of course, that this competition perspective is of critical importance in the FOB debate – which is why we are grateful to have been given, literally, a seat at this table today.

If Congress can create a balanced pathway for FOBs, and also pass legislation to eliminate "pay-for-delay" patent settlements between branded and generic companies in small-molecule markets, Congress will have taken substantial steps to ensure that all Americans have access to affordable, life-saving medicines. On behalf of Chairman Leibowitz, I commend the Committee for moving legislation to ban these patent settlements through the Consumer Protection Subcommittee last week.

Overview of Testimony

The report's basic premise is that competition between pioneer biologics and FOBs is likely to look much more like current competition between two or more branded drugs that

treat the same medical condition – for example, Enbrel and Remicade, which both treat rheumatoid arthritis. It will look less like current competition between branded and generic versions of a drug.

I will explain why the Commission reached this conclusion, and I will also identify some implications for legislation seeking to create an abbreviated regulatory approval pathway for FOBs.

Key Characteristics of the Biologics Marketplace

But first, I will begin by highlighting some important characteristics of the biologics marketplace.

As you know, the emergence of biologic drugs has dramatically improved the lives of thousands of Americans over the past few decades. For example, the biologic “*Herceptin*” is used to treat breast cancer, and an annual course of treatment costs about \$48,000.

One way to reduce the costs of biologics would be to authorize the Food and Drug Administration (FDA) to permit follow-on biologics, or FOBs, to enter the market once a biologic drug’s patents expire. However, there is no statutory or regulatory pathway to allow abbreviated FOB entry without the FOB applicant having to duplicate existing knowledge about safety and efficacy. This duplication represents an inefficient use of limited R&D resources. Also, as the FDA has explained, repeating all of the clinical trials raises ethical concerns associated with unnecessary human testing.

Elements of the Hatch-Waxman Act provide a model for reducing FOB entry costs and addressing ethical concerns. Hatch-Waxman does not require generic applicants to duplicate the clinical testing of branded drugs that already have been proven safe and effective. Hatch-Waxman has successfully reduced drug prices, broadened access, and hastened the pace of innovation. And if pay-for-delay settlements are prohibited, these benefits of Hatch-Waxman will be preserved.

But as the report describes, according to the FDA, there are key scientific differences between biologic and small-molecule drug products. Most notably, under Hatch-Waxman, the generic applicant must show that its product is “bioequivalent” to the branded drug product. This is important because it means that the product is identical.

In stark contrast, according to the FDA, biologic products cannot be perfectly duplicated – at least not based on current science. Technology is not yet robust enough to determine whether an FOB product is “interchangeable” with the pioneer product.

Current FOB legislative proposals reflect the complexities of biologics. They would permit FDA approval of an FOB drug that is *similar* to, but not an exact replica of, the pioneer biologic product. Under these proposals, the FDA could rely on its previous findings regarding the pioneer biologic drug's safety and efficacy, to the extent those findings also would be relevant to the FOB. An FOB manufacturer likely would save on some clinical testing expenses, which would reduce entry costs.

The Commission's Study Objectives

With that background in mind, let me turn to the Commission's report. The purpose of our study was to evaluate how FOB competition is likely to develop and evolve, paying particularly close attention to the differences between small-molecule and biologic drugs.

The study was coordinated by an interdisciplinary FTC team (headed by Mr. Wroblewski) that included not only pharmaceutical industry experts, but also patent lawyers and economists. As part of its inquiry, the Commission solicited two rounds of public comments, which attracted submissions from approximately 30 industry participants and other stakeholders.

In November 2008, the Commission conducted a public roundtable discussion that included over 30 panelists. The Commission also has examined European markets where FOB entry has occurred.

The Commission's Findings Regarding FOB Competition

In the interest of time, let me briefly summarize the four major reasons why FOB competition will not be like generic drug competition.

- First is the extraordinary cost and time necessary to develop an FOB, which will sharply limit the number of competitors who can afford to enter, and also will limit the discounts the FOB can offer in relation to the pioneer price.
 - FOB products are likely to take eight to ten years to develop, and their development likely will cost between \$100 and \$200 million each.
 - In contrast, small-molecule generic drugs typically take three to five years to develop, with product development costs of between \$1 and \$5 million, and much lower manufacturing costs as well.
 - In addition, it is expected to cost between \$250 million to \$1 billion to build a new biologic manufacturing plant.

- Second, follow-on entry will not radically erode the pioneer's market share.
 - In the small-molecule space, when lower-cost interchangeable generics enter, the branded firm soon loses most of its share as patients switch to generics.
 - But in biologics, a pioneer is likely to retain significant market share after FOB entry, largely due to the pioneer's first-mover advantage, the lack of interchangeability, no automatic substitution, and a smaller price discount.
- Third, the specialty pharmaceutical characteristics of FOBs are likely to further constrain the FOB entrant's ability to gain market share.
 - Specialty drugs are primarily injected or infused, and they are combined with ancillary medical services and products that require specialized training for proper handling and administration.
 - These factors will make it more difficult to switch from a pioneer to an FOB alternative.
- Finally, because biologics are provided in clinic-type settings as part of medical treatments, they are not purchased and reimbursed in the same manner as small-molecule drugs.

As a result of all of these factors, the Commission's report predicts that FOB markets are likely to develop with the following characteristics.

- FOB entry is likely to occur only in biologic drug markets with more than \$250 million in annual sales.
- Only two or three FOB manufacturers are likely to attempt entry in competition with a particular pioneer drug product.
- These FOB entrants likely will not offer price discounts larger than 10% to 30% off the pioneer product's price. Although this discount is not as steep as with small-molecule generic drugs, it does represent millions of dollars in consumer savings for these very expensive products.
- Pioneer manufacturers are expected to respond by offering competitive discounts to maintain their market share. This price competition likely will increase consumer access and further expand the market.

- Without automatic substitution, FOB market share acquisition will be slowed. Pioneer manufacturers likely will retain 70% to 90% of their market share. This means that a pioneer firm will continue to reap substantial profits for years, even after entry by an FOB.

FOB market dynamics will contrast sharply with the market dynamics of generic drug competition, where lower-cost generic entry plus automatic substitution lead to rapid erosion of the branded drug's market share. When the first generic drug enters the market, it generally offers a 25% discount off the branded drug's price. As additional generic firms enter – and often there are eight or more of them – the price discounts reach as high as 80%.

Incentives That Support Innovation and Competition: Patent Protection Plus Market-Based Pricing

Given these likely dynamics of FOB markets, the Commission next asked whether any additional incentives will be needed to encourage FOB competition and foster ongoing biologics innovation. The report concludes that existing incentives – the same ones that motivate branded biologics – are sufficient. These two incentives are patent protection and market-based pricing.

Through patent protection and the resulting exclusionary rights – biotech firms increase their expected profits from investments in R&D. Patents thus foster innovation that would not otherwise occur.

Market-based pricing allows firms to charge prices that reflect the value of the drugs to consumers. By pricing at market rates, firms can recoup their substantial investments in biologic drugs. Prices also enable firms to receive accurate market signals about the value of developing particular biologic drugs.

Currently, pioneer drug manufacturers race against other firms to bring products to market, in both pharmaceuticals and biologics. This competition benefits consumers by accelerating the pace of innovation, and also through eventual price competition. Given that FOB competition is likely to resemble competition by another brand, FOB competition is likely to promote the same consumer benefits, without the need for any additional incentives.

Implications for FOB System Design

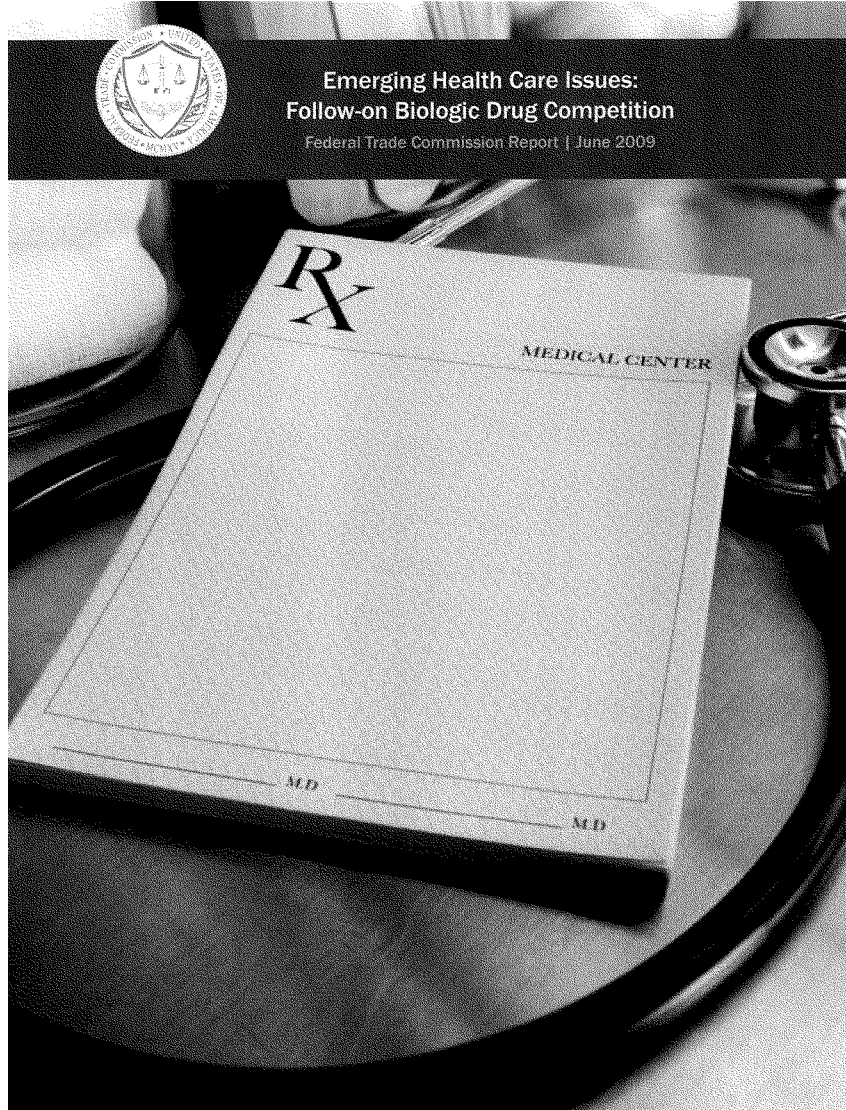
These findings have several implications for the design of an abbreviated approval system for FOBs. In the interest of time, I will briefly summarize three key implications. Mr. Wroblewski and I are happy to elaborate further during the question period.

- First, pioneer manufacturers are unlikely to need additional incentives to continue to innovate in the face of FOB entry, beyond existing patent protection and market-based pricing.
 - It appears that pioneer biologics are capable of being covered by numerous and varied patents, including manufacturing and technology platform patents.
 - There is no evidence that patents claiming a biologic drug product have been, or are likely to be, designed around more frequently than those claiming small-molecule products.
 - Market-based pricing – especially during the period of exclusivity granted by the patent system itself – provides strong incentives to innovate.
 - In light of these existing patent incentives, the Commission report concludes that no additional period of branded exclusivity is needed to spur the development of new drug products.
 - To the extent that drugs are unpatentable, an exclusivity period could be used to incentivize their clinical testing.
- A second implication is that it is unnecessary to implement special procedures to resolve patent issues between pioneer and FOB drug manufacturers.
 - The Hatch-Waxman procedures to trigger an early start of patent litigation made sense in the generic drug context, where there was a concern that generics would not be able to pay post-entry patent infringement damages.
 - But looking at the cost and complexity of bringing FOBs to market, it is likely that only well-funded firms will seek FOB entry, which will mitigate concerns about the enforceability of patent infringement judgments.
 - Moreover, special procedures are unlikely to succeed in raising and resolving all pertinent patent issues prior to FDA approval, and may create competitive problems.
- Third, FOB drug manufacturers are unlikely to need additional incentives to develop interchangeable FOB products, such as a marketing exclusivity period for the first FOB.

- If FOB competition will closely resemble brand-to-brand competition, then the incentives provided by market-based pricing should be sufficient, and there is no reason to risk delaying the entry of subsequent FOBs that are ready for market.

Conclusion

Again, thank you for the opportunity to present the Commission's report. Mr. Wroblewski and I will do our best to respond to your questions.



FEDERAL TRADE COMMISSION

JON LEIBOWITZ	Chairman
PAMELA JONES HARBOUR	Commissioner
WILLIAM E. KOVACIC	Commissioner
J. THOMAS ROSCH	Commissioner

Joni Lupovitz	Chief of Staff
Charles H. Schneider	Executive Director
Richard Feinstein	Director, Bureau of Competition
Jeanne Bumpus	Director, Office of Congressional Relations
Susan S. DeSanti	Director, Office of Policy Planning
Donald S. Clark	Secretary of the Commission

Report Drafters and Contributors

Michael S. Wroblewski, Deputy Director, Office of Policy Planning
 Elizabeth A. Jex, Bureau of Competition
 Suzanne Drennon Munck, Bureau of Competition
 Christopher J. Garmon, Bureau of Economics
 Suzanne T. Michel, Assistant Director, Office of Policy Coordination,
 Bureau of Competition
 Alissa Wantman, Bureau of Competition
 Ossie L. Neal, Bureau of Competition

Inquiries concerning this report should be directed to:
 Michael S. Wroblewski (202) 326-2435 or mwroblewski@ftc.gov

EXECUTIVE SUMMARY

Over the past three decades, the lure of patent protection, coupled with the ability to price at market rates, has spurred pioneer drug manufacturers to develop new therapeutic drugs known as biologics. These innovations have improved medical treatments, reduced suffering, and saved the lives of many Americans. Biologic drugs are protein-based and derived from living matter or manufactured in living cells using recombinant DNA biotechnologies. The therapeutic proteins that form the basis of these biologic drugs are far more complex and much larger than the chemically synthesized, small molecules that form the basis of most pharmaceutical products.

Biologic drug innovations, however, are expensive. As examples, annual treatment for breast cancer with the biologic drug Herceptin can cost \$48,000 and the annual treatment for rheumatoid arthritis with Remicade can cost approximately \$20,000. Indeed, in 2007, Americans spent \$286.5 billion for prescription drugs, \$40.3 billion of which was for biologic drugs.¹

Questions have arisen whether the price of biologics might be reduced by competition if there were a statutory process to encourage “follow-on biologics” (“FOBs”) to enter and compete with pioneer biologics once a pioneer drug’s patents have expired. The obvious model for such a statute is the Hatch-Waxman Act, which Congress enacted in 1984 to allow the Food and Drug Administration (“FDA”) to approve the sale of generic versions of branded drugs, among other things.² The Hatch-Waxman Act does not apply to biologics, which the FDA approves pursuant to the Public Health Safety (“PHS”) Act. Rather, Hatch-Waxman applies only to drugs regulated under the Federal Food Drug and Cosmetic Act (“FD&C Act”); these drugs are generally chemically synthesized, small-molecule products, not biologics.

Under Hatch-Waxman, competition from generic drugs has substantially reduced prescription drug prices and overall prescription drug expenditures, increased access to therapeutic drugs for more Americans, and hastened the pace of innovation.³ In recent years, however, several court decisions have permitted “pay-for-delay settlements” that have reduced the procompetitive aspects of the Hatch-Waxman Act. The Commission supports legislation to prohibit these types of settlements in which the branded manufacturer pays the would-be generic

¹ These sales figures are based on wholesale prices reported in the IMS Top Line Industry Data. Press Release, IMS Health, IMS Health Reports U.S. Prescription Sales Jump 3.8 Percent in 2007, to \$286.5 Billion (March 12, 2008), available at <http://www.imshealth.com> (follow “Press Room” hyperlink; then follow “IMS Health Care Reports News Release” hyperlink).

² See The Federal Food, Drug, and Cosmetic Act, 21 U.S.C.A. § 301 *et seq.* (2009), as amended by the Drug Price Competition and Patent Term Restoration Act of 1984 (the “Hatch-Waxman Act” or “Hatch-Waxman”) and the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, 21 U.S.C.A. § 355(j) (2009) and 35 U.S.C.A. § 271(e) (2009) [United States Code Annotated].

³ See generally Jennifer S. Haas, et al., *Potential Savings from Substituting Generic Drugs for Brand-Name Drugs: Medical Expenditure Panel Survey, 1997-2000*, 142 ANNALS INTERNAL MED. 891 (June 2005); Wendy H. Schacht and John R. Thomas, Congressional Research Service (CRS), Library of Congress, *Report for Congress, Follow-On Biologics: Intellectual Property and Innovation Issues*, at 4 & 18, 110th Cong. (Jan. 17, 2008), available at http://www.biosimilars.com/CRS_FOBs.pdf.

entrant to abandon its patent challenge and delay entering the market with a lower cost, generic product.⁴

Hatch-Waxman does not require generic applicants to duplicate the clinical testing of drugs already proven safe and effective. Duplication of safety and efficacy information is costly, an inefficient use of scarce resources, and, as the FDA has explained, raises ethical concerns associated with unnecessary human testing.

To be approved under Hatch-Waxman, the applicant must show that its generic drug product is “bioequivalent” to (basically, the same as) the branded drug product. A bioequivalence showing is much less expensive than the clinical testing required for a branded drug product. Because the generic drug is “bioequivalent” to the branded drug, it can be safely substituted for the branded drug and expected to be as effective as the branded drug. To take advantage of generic competition, states have laws that allow pharmacists automatically to substitute a generic for a branded drug, unless a doctor has indicated otherwise.

The scientific differences between biologic and small-molecule drug products, however, complicate efforts to devise an approval process for FOB drugs based on bioequivalence. Biologic products are more complex and immunogenic than small-molecule drugs.⁵ Current technology does not yet allow for the creation of an exact replica of a pioneer biologic drug product, according to the FDA. In addition, technology is not yet robust enough to determine whether an FOB product is “interchangeable” with the pioneer product such that a patient would be able to switch between the two products without the risk of an adverse effect. In light of these complexities, current legislative proposals permit FDA approval of an FOB drug that is sufficiently *similar* to, but not an exact replica of, the pioneer biologic product.⁶ A showing of similarity is likely to save FOB manufacturers some clinical testing expenses but would require substantially more expense than a showing of bioequivalence for small-molecule generic drugs.

Whether competition between a pioneer biologic and an FOB is likely to be similar to competition between a branded and a generic drug is crucial to determining whether legislation to foster FOB competition should follow the same model as the Hatch-Waxman Act. Basic questions include whether the same issues that prompted provisions of the Hatch-Waxman Act that restrict entry by generic competitors are likely to be present in the context of FOB competition. To answer these questions, the Commission studied how competition between

⁴ See *How Pay-for-Delay Settlements Make Consumers and the Federal Government Pay More for Much Needed Drugs: Hearing Before the H. Subcomm. on Commerce, Trade, and Consumer Protection, Comm. on Energy and Commerce*, 111th Cong. (2009) (Prepared Statement of the Federal Trade Commission), available at <http://www.ftc.gov/os/2009/03/P859910payfordelay.pdf>.

⁵ Immunogenicity raises safety and effectiveness concerns because of a biologic drug’s ability to stimulate an immune response. See Letter from Frank M. Torti, Principal Deputy Comm’r and Chief Scientist, FDA, to Frank Pallone, Jr., Chmn., H. Subcomm. on Health, (Sept. 18, 2008) at 1, available at http://energycommerce.house.gov/Press_110/fdabiosimilarrespons20080918.pdf.

⁶ See H.R. 1427, 111th Cong. § 3(a) (2009); H.R. 1548, 111th Cong. § 101 (2009).

pioneer biologics and FOBs is likely to develop to determine whether similar entry restrictions would benefit consumers.

The Commission brings substantial expertise to examining likely models of competition and likely competitive effects from particular regulatory schemes.⁷ To assist in its study of the issues, the Commission solicited two rounds of public comments, conducted a public roundtable discussion on November 21, 2008, and accepted additional analysis and comments through May 2009. This report analyzes and synthesizes the Roundtable discussion, the comments received, and relevant economic literature to assess these issues. The Commission's findings and recommendations follow.

1. Competition Between a Biologic Drug and an FOB is Much More Likely to Resemble Brand-to-Brand Competition than the Dynamics of Brand-Generic Competition under Hatch-Waxman.

Pioneer manufacturers, potential FOB manufacturers, and payors were virtually unanimous in their predictions that competition from FOB drug entry is likely to resemble brand-to-brand competition, rather than brand-to-generic drug competition. Experience to date for two markets with both pioneer biologic and FOB competitors (in Europe and the U.S.) confirms that, unlike generic drug entry, FOB entry has not resulted in steep price discounting, or rapid acquisition of market share, by FOB manufacturers.⁸ This finding is true for a number of reasons:

- **The substantial costs to obtain FDA approval, plus the substantial fixed costs to develop manufacturing capacity, will likely limit the number of competitors that undertake entry with FOB products.** FOB products are likely to take eight to ten years to develop, and their development will likely cost between \$100 and \$200 million. These amounts differ substantially from the product development costs for small-molecule generic drugs, which typically take three to five years to develop and cost between \$1 and \$5 million.
- **Given these high entry costs, FOB entrants are likely to be large companies with substantial resources, and it is likely that only two to three FOB entrants will seek**

⁷ The Commission has reviewed pharmaceutical and biotechnology mergers for over 30 years, and has conducted numerous investigations and enforcement actions involving the conduct of branded and generic small-molecule drug manufacturers arising in the context of the Hatch-Waxman Act. See <http://www.ftc.gov/be/0608rxupdate.pdf>. The Commission also conducted a detailed empirical study of the experience during the 1993-2001 under the Hatch-Waxman Act's procedures designed to facilitate entry of generic drugs. Federal Trade Commission, *Generic Drug Entry Prior to Patent Expiration: An FTC Study* (July 2002). Since 2004, FTC staff has reviewed every drug company patent settlement filed under Hatch-Waxman, and issued annual reports on the types of patent settlements being undertaken. The reports are available at <http://www.ftc.gov/be/healthcare/drug/index.htm>.

⁸ Historically, some biologic protein products have been regulated as drugs under the FD&C Act, including insulin, and human growth hormones. The FDA has approved six follow-on protein products under the FD&C Act. See *Assessing the Impact of a Safe and Equitable Biosimilar Policy in the United States Hearing Before H. Subcomm. on Health and the H. Comm. on Energy and Commerce*, 110th Cong. (2007) (statement of Janet Woodcock, Deputy Comm'r, Chief Medical Officer, FDA), available at http://energycommerce.house.gov/cmte_mtgs/110-he-hrg.050207.Woodcock-testimony.pdf.

approval to compete with a particular pioneer biologic drug. Current pioneer biologic drug manufacturers are likely to become FOB competitors in those markets in which they do not currently compete. Moreover, high entry costs are likely to limit FOB drug entry to markets with sales in excess of \$250 million per year. The small number of likely FOB entrants contrasts significantly with the 10 or more generic entrants seen in many markets for small-molecule drugs.

- **The lack of automatic substitution between an FOB product and a pioneer biologic drug will slow the rate at which an FOB product can acquire market share and thereby increase its revenues.** In small-molecule drug markets, automatic substitution erodes a branded manufacturers' market share quickly once the first generic product enters the market. This situation is unlikely to occur in FOB markets. Unlike small-molecule generic drugs, FOB products will not be designated as "therapeutically equivalent" with the pioneer biologic drug product. The lack of therapeutic equivalence means that, like pioneer manufacturers, FOB manufacturers will have to market their products and negotiate individual contracts with purchasers.
- **An FOB drug also may have difficulty gaining market share due to concerns about safety and efficacy differences between a pioneer biologic drug and the competing FOB.** Physicians and their patients who have been taking a pioneer biologic drug may be reluctant to switch to an FOB due to a risk that the patients will react differently to the FOB than to the pioneer drug. Concerns such as these may limit FOB market opportunities to newly diagnosed patients.
- **The specialty pharmaceutical characteristics of FOBs also are likely to constrain the ability of an FOB entrant to obtain market share.** Specialty drugs, including biologic drugs, are commonly used to treat patients with severe, chronic diseases and sometimes fatal conditions. These drugs, which are primarily injected or infused, are combined with ancillary medical services and products that require specialty training for proper handling and administration. Because most biologic products are delivered to patients in clinics, hospitals, doctor's offices, or other medically supervised settings, shifting to another biologic product is typically more costly because it requires restocking of inventory and retraining of nurses and healthcare providers.
- **Biologic drugs currently are not reimbursed pursuant to strategies that payors often use to incentivize the use of lower-priced drugs; this, too, may limit market share acquisition by FOBs.** Biologic drug products are typically delivered to patients by healthcare providers as part of medical treatments (e.g., dialysis treatments or oncology treatments) and reimbursed by health insurers as part of patients' medical benefits rather than pharmacy benefits. Consequently, traditional payor strategies to incentivize utilization of lower-priced drugs, including the use of co-pays and tiered formularies, are unlikely to apply to drive up the market share of FOBs. FOB pricing and market shares also are likely to be affected by the reimbursement methodologies used by Centers for Medicare and Medicaid Services ("CMS") for infused and injected drugs, which may not effectively drive share to lower-priced drugs.

- **As a result of these factors, FOB competition against a pioneer biologic drug is likely to develop as follows:** FOB entry is likely in biologic drug markets of greater than \$250 million. Only two or three FOB manufacturers are likely to attempt entry for a given pioneer drug product. These FOB entrants are unlikely to introduce their FOB products at price discounts any larger than between 10 and 30 percent of the pioneer products' price. Although not as steep a discount as small-molecule generic drugs, a 10 to 30 percent discount on a \$48,000 drug product represents substantial consumer savings. Pioneer manufacturers are expected to respond and offer competitive discounts to maintain market share. This price competition is likely to lead to an expanded market and greater consumer access. Nonetheless, the lack of automatic substitution will slow significant market share acquisition by FOB products. As a result, pioneer manufacturers are likely to retain 70 to 90 percent of their market share and, therefore, will likely continue to reap substantial profits years after entry by FOB drugs.
- 2. Existing Incentives that Support Brand-to-Brand Competition Among Biologic Drugs – Patent Protection and Market-Based Pricing – Are Likely to be Sufficient to Support FOB Competition and Biologic Innovation.**

A legislative process for an abbreviated FDA approval of an FOB is likely to be an efficient way to bring FOBs to market because of the time and cost savings it provides. Given that FOB competition with a pioneer biologic drug is likely to resemble brand-to-brand competition among biologics, the question arises whether provisions that delay FOB entry and restrict competition are necessary to benefit consumers. No economic arguments suggest that such provisions are necessary to foster pioneer drug innovation or entry of interchangeable FOBs.

Brand-to-brand competition among biologics has developed without any special legislative incentives, but rather through reliance on the patent system and market-based pricing. Patent protection enables biotechnology firms to increase their expected profits from investments in R&D, thus fostering innovation that would not occur without patents' exclusionary rights.⁹ Market-based pricing allows biologic drug firms to charge prices that reflect the value of the drugs to consumers and thus assists firms not only in recouping their substantial investments in biologic drugs, but also in receiving accurate market signals about the value of developing particular biologic drugs.

Market experience shows that pioneer pharmaceutical and biologic products already compete against other branded pharmaceutical and biologic entrants, and this competition benefits consumers. Currently, pioneer or first-in-class branded products engage in a race with other branded competitors to bring products to market.¹⁰ It is likely that FOB competition similarly will develop without any special legislative incentives.

⁹ F.M. Scherer & David Ross, *INDUSTRIAL MARKET STRUCTURE AND ECONOMIC PERFORMANCE*, 3d Ed. 621 (1990).

¹⁰ See Joseph DiMasi & Cherie Paquette, *The Economics of Follow-on Drug Research and Development*, 22 *PHARMACOECONOMICS* Supp 2:1-14, 10 (2004). Although this study examined pharmaceutical products primarily, it included several biologic drugs as well.

Indeed, any decision to adopt special legislative incentives that restrict competition may harm consumers. The Commission is mindful that the benefits of suppressing rivalry by either pioneer or FOB manufacturers are realized by a comparatively small number of firms who fully understand the importance of restricting competition. By contrast, the costs of restricting competition tend to be spread broadly across a large number of consumers, each of whom suffers a comparatively modest penalty compared to the relatively substantial gain realized by incumbent producers.¹¹ The phenomenon of highly focused benefits and broadly distributed costs gives firms a greater incentive to organize political resources to restrict competition.

a. A Twelve- to Fourteen-Year Exclusivity Period is Unnecessary to Promote Innovation by Pioneer Biologic Drug Manufacturers.

As explained earlier, pioneer biologic drug manufacturers are very likely to continue to earn substantial revenues even after the entry of FOBs. FOBs are unlikely to introduce their products at price discounts beyond 10 to 30 percent. Moreover, FOBs are likely to have difficulty rapidly growing their market shares as compared to generic small-molecule drug products. Indeed, projections are that branded biologic drugs are likely to maintain their first-mover advantages by retaining 70 to 90 percent of their market share years after FOB entry.

In addition, there is very little data to suggest that biologic drugs under development are likely to be unpatentable. Pioneer biologic drugs are covered by more and varied patents, including manufacturing and technology platform patents, than small-molecule branded products. Moreover, there is no evidence that patents claiming a biologic drug product have been designed around more frequently than those claiming small-molecule products.

Pioneer biologic manufacturers nevertheless have suggested that Congress institute a period of 12 to 14 years of branded exclusivity that would begin once a pioneer biologic was approved by the FDA.¹² During this period, the FDA would be prohibited from approving an FOB product that would compete with the pioneer biologic drug. This branded exclusivity would be in addition to, and would run concurrent with, a biologic drug's existing patent protection. The economic model put forth by pioneer drug manufacturers to justify this period is

¹¹ See Organization for Economic Co-operation and Development, *Challenges Obstacles Faced by Competition Authorities in Achieving Greater Economic Development Through the Promotion of Competition, Contribution from the United States* (Feb. 5, 2004), available at <http://www.scribd.com/doc/1170395/US-Federal-Trade-Commission-2004Challenges20Obstacles20aced20by20Competition>.

¹² This report uses the term "branded exclusivity" rather than "data exclusivity" because current legislative proposals permit an FOB applicant to rely on FDA's finding or conclusion that an approved pioneer drug is safe and effective. This reliance does not involve disclosure to the FOB applicant, or to the public, of the data in the pioneer manufacturers' application. See Letter from Director Steven K. Glason, Center for Evaluation and Research ("CDER"), FDA to Petitioners (May 30, 2006) at 6, available at <http://www.fda.gov/ohrms/dockets/dockets/04P0231/04P-0231-pdn0001.pdf>. The term "data exclusivity" suggests a use of the information that is inconsistent with FDA's longstanding interpretation of its approval process.

based on the average time required to recoup the investment to develop and commercialize a typical biologic drug (referred to as the “Nature model”).¹³

Congress has implemented exclusivity provisions in the past to encourage the development of new and innovative drug products when the drug molecule is in the public domain, and therefore not patentable. The Hatch-Waxman Act provides a five-year exclusivity period to incentivize the development of new chemical entities and it provides a three-year exclusivity period for new clinical investigations of small-molecule drugs. In other instances, Congress has implemented an exclusivity period when market-based pricing has not provided sufficient incentive to develop drug products for children or small patient populations.

Central to each of these exclusivities is a public policy trade-off: a restriction on competition is provided in return for the development of a *new* drug product or *new* use of an existing product. A 12- to 14-year exclusivity period departs sharply from this basic trade-off, because it does not spur the creation of a *new* biologic drug or indication. The drug has already been incentivized through patent protection and market-based pricing.

The potential harm posed by such a period is that firms will direct scarce R&D dollars toward developing low-risk clinical and safety data for drug products with proven mechanisms of action rather than toward new inventions to address unmet medical needs. Thus, a new 12- to 14-year exclusivity period imperils the efficiency benefits of a FOB approval process in the first place, and it risks over-investment in well-tilled areas.

The Nature model as currently structured contains numerous methodological and conceptual weaknesses that render its results too imprecise and non-robust to inform discussions about the ideal length of any branded exclusivity period. A model that balances the benefits of FOB competition (*i.e.*, lower prices and an increased pace and scope of innovation) with the costs of potentially forsaking marginal branded drug development projects would be more informative than the Nature model’s approach.

Moreover, to the extent that there are new biologic molecules that cannot obtain patent protection, an exclusivity period may be warranted. Because there is no evidence about the lack of patentability of new biologic products, nor that market forces have been insufficient to incentivize their development, the Commission has not recommended a specific length for an exclusivity period.

b. Special Procedures to Resolve Patent Issues Between Pioneer and FOB Drug Manufacturers Prior to FDA Approval Are Unnecessary and They Could Undermine Patent Incentives and Harm Consumers.

Once a pioneer biologic drug manufacturer receives FDA approval and is about to market its product, it faces the risk of patent infringement litigation. FOB manufacturers are likely to face the same risk. If they believe the patent situation justifies their decisions to launch prior to

¹³ Henry C. Grabowski, *Follow-on Biologics: Data Exclusivity and the Balance Between Innovation and Competition*, 7 NATURE REVIEWS DRUG DISCOVERY 479, 483 (June 2008).

resolution of any patent infringement litigation, they will enter once they have received FDA approval. If not, they will wait for the patents to expire and then launch their product. Special procedures, providing an early start to resolving patent disputes between pioneer and FOB manufacturers prior to FDA FOB approval, are not necessary to encourage FOB entry that otherwise would not have occurred.

Hatch-Waxman's special procedures for small-molecule drugs provide for an early start of patent litigation. Hatch-Waxman procedures have been the subject of extensive litigation, unintended consequences, and delayed generic entry. These procedures were designed in 1984 to address the issue of "judgment proof" generic defendants. In small-molecule drug competition, the profits of the alleged infringer (the generic entrant) are substantially less than the loss of profits by the branded product manufacturer, because of the substantial price differences between branded and generic products. Consequently, especially at the beginning of the generic industry in 1984, concerns existed that generic entrants in small-molecule drug markets might be unable to satisfy a potential treble damage award for infringing the branded manufacturer's patents.

FOB entrants will not be similarly judgment proof. FOB drug manufacturers are likely to be many of the same companies that have pioneered biologic drugs; thus, they will have the expertise and resources necessary to assess whether to launch their product before any patent infringement litigation is resolved, just as they do with a launch of a pioneer branded drug. Moreover, FOB manufacturers are highly unlikely to offer steep discounts that could jeopardize their ability to pay patent damages.

Special procedures are unlikely to be successful in providing patent certainty to the parties, because pioneer biologic drugs are covered by more and varied patents than small-molecule drugs. A special pre-approval patent resolution process is unlikely to succeed in raising and resolving all pertinent patent issues prior to FDA approval. Patents claiming the pioneer product may issue after a pre-approval process has begun and/or after FDA approval. The FOB manufacturer's application and product also may change during the approval process such that starting patent litigation prior to FDA approval would not ensure earlier resolution. Moreover, without a mechanism to enforce the rules of a pre-approval resolution process, there is no guarantee that litigation started prior to FDA approval will end earlier. In essence, early start does not guarantee early resolution.

Special procedures also could undermine the innovation incentives that patent protection affords pioneer biologic manufacturers. Although special procedures govern patent litigation between branded and generic competitors over small-molecule drug products, these procedures are the exception, not the norm.

Finally, based on the experience under Hatch-Waxman, a pre-approval patent resolution process also is likely to lead to consumer harm, including the facilitation of anticompetitive conduct that defeats the purpose of starting the patent litigation early. In the Hatch-Waxman context, branded manufacturers have used the pre-approval patent regulations to delay generic entry. In addition, generic and branded competitors have entered into "pay-for-delay" patent settlements that delay entry, not encourage it. It is likely that a pre-approval patent resolution

process in the FOB context could facilitate collusive agreements and/or provide the pioneer biologic drug manufacturer with competitively sensitive information about a significant potential competitor to which it otherwise would not have access.

c. FOB Drug Manufacturers Are Unlikely to Need Additional Incentives to Develop Interchangeable FOB Products.

The question arises whether an FOB manufacturer needs an incentive beyond market-based pricing to develop an interchangeable FOB drug, such as a limit on when subsequent interchangeable FOB drug entry can occur. This limitation would allow the first interchangeable FOB manufacturer to recoup its development expenses. Because the market dynamics of FOB entry are likely to resemble competition among branded biologic drugs, provisions modeled after the Hatch-Waxman Act's 180-day marketing exclusivity are unlikely to be necessary and, indeed, could harm consumers.

The Hatch-Waxman Act provides a 180-day marketing exclusivity period to the first generic drug applicant that seeks FDA approval prior to the expiration of patents relating to the branded drug product. No other generic manufacturer may obtain FDA approval to market its product until the first generic has sold its product for 180 days or has forfeited its exclusivity period.

The 180-day exclusivity period incentivizes generic manufacturers to challenge the patents claiming a pioneer small-molecule drug product. A court finding of patent invalidity benefits not only the challenger, but also subsequent generic applicants whose entry is no longer blocked by the patent. Thus, the 180-day marketing exclusivity period prevents immediate free-riding by subsequent generic applicants on a favorable outcome that results from a generic applicant's patent challenge. As subsequent generic firms enter, generic prices can drop to 80 percent off the branded price, depending upon the number of entrants.¹⁴ The exclusivity period is supposed to permit the first generic entrant to recoup its patent litigation costs before the substantial price drop caused by multiple generic entrants.

The competitive dynamics that justified the 180-day exclusivity period for small-molecule generic drugs are unlikely to be present here, because the entry of a subsequent interchangeable FOB is unlikely to cause a substantial price drop due to the high costs of developing and manufacturing and FOB. The first interchangeable FOB to enter will continue to earn sufficient profits even after entry of subsequent interchangeable products. Thus, market opportunities are likely to be sufficient to incentive development of interchangeable FOBs.

Not only do market dynamics counsel against an FOB exclusivity period, but the anticompetitive delay in entry evidenced in small-molecule generic drug markets is likely to

¹⁴ See David Reiffen & Michael Ward, "Branded Generics" As A Strategy To Limit Cannibalization of Pharmaceutical Markets, 28 MANAGERIAL AND DECISION ECONOMICS, 251-265, 264 (2005), available at http://ftc.gov/be/healthcare/wp/12_Reiffen_BrandedGenericsAsAStrategy.pdf.

repeat if an exclusivity provision for interchangeable FOBs is implemented.¹⁵ The current 180-day exclusivity period exacerbates the problem of “pay-for-delay” settlement that prevents generic entry.¹⁶

Awarding an FOB exclusivity period on a “first-to-approve” rather than a “first-to-file” basis does not lessen the potential harm. These anticompetitive consequences are likely to result if the period can be extended, the period does not run immediately upon its award, or if a firm has the ability to delay triggering the running of the period through, for example, a patent settlement, acquisition, merger, or agreement.

¹⁵ See FDA, Center for Drug Evaluation and Research, 180-Day Generic Drug Exclusivity (2001), available at http://www.fda.gov/cder/about/smallbiz/generic_exclusivity.htm#COURT (“This 180-day exclusivity provision has been the subject of considerable litigation and administrative review in recent years...”).

¹⁶ See *How Pay-for-Delay Settlements Make Consumers and the Federal Government Pay More for Much Needed Drugs: Hearing Before the H. Subcomm. on Commerce, Trade, and Consumer Protection, Comm. on Energy and Commerce*, 111th Cong. (2009) (Prepared Statement of the Federal Trade Commission), available at <http://www.ftc.gov/os/2009/03/P859910payfordelay.pdf>.

TABLE OF CONTENTS

EXECUTIVE SUMMARY	i
INTRODUCTION.....	1
CHAPTER 1 BACKGROUND AND LIKELY MARKET IMPACT OF FOLLOW-ON BIOLOGIC COMPETITION	3
I. BACKGROUND.....	3
II. THE NEW DRUG AND GENERIC DRUG APPROVAL PROCESS	6
A. New Drug Approval Processes Under the FD&C Act and the PHS Act...	6
B. Generic Drug Approval Under the FD&C Act.....	7
C. Issues in Translating the Generic Drug Approval Process to Biologic Drugs Under the PHS Act.....	8
III. PHARMACEUTICAL PRICING, MARKET DYNAMICS, AND THE LIKELY COMPETITIVE IMPACT OF FOLLOW-ON BIOLOGICS.....	10
A. Pharmaceutical Pricing and the Effect of Generic Drug Entry.....	11
B. Likely Market Effects of Biosimilar Entry.....	13
1. Fewer FOB Competitors Due to High Barriers to Entry.....	14
2. Lack of Interchangeability.....	16
3. Specialty Pharmaceutical Characteristics.....	17
4. Fewer Payor Strategies to Incentivize Rapid Uptake of FOBs.....	17
C. Market Experience with Biosimilar Entry.....	19
1. EPO Market Experience in the European Union.....	20
2. HGH Market Experience in the European Union and the United States.....	21
D. Likely Pricing Effect of Interchangeable FOBs.....	22
E. Conclusions about the Likely Market Impact of FOB Entry.....	23

CHAPTER 2	PATENT PROTECTION AND MARKET INCENTIVES ARE LIKELY TO CONTINUE TO PROVIDE ROBUST INNOVATION INCENTIVES AFTER ENTRY OF FOLLOW-ON BIOLOGIC DRUGS.....	25
I.	INTRODUCTION.....	25
II.	THE IMPORTANCE OF PATENT PROTECTION TO THE NEW DRUG RESEARCH AND DEVELOPMENT PROCESS.....	28
A.	New Drug Research and Development Process.....	28
B.	The Importance of Patent Protection Incentives for Innovation.....	30
C.	Patent Protection in the Biotechnology Industry.....	32
1.	Panelists' and Commenters' Arguments that Patents Are Unlikely to Incentivize Innovation in Light of FOB Competition.....	32
2.	Panelists' and Commenters' Arguments that Patent Protection Provides Ample Incentives for Innovation.....	34
D.	Patent Protection is Likely to Continue to Provide Strong Incentives for Innovation after Introduction of Follow-On Drug Competition.....	35
III.	OTHER CONSIDERATIONS DO NOT SUPPORT A 12- TO 14-YEAR BRANDED EXCLUSIVITY PERIOD.....	39
A.	Panelists' and Commenters' Views on the Likely Effects of a Branded Exclusivity Period.....	39
B.	Panelists' and Commenters' Views on the Need for Branded Exclusivity to Incentivize Incremental Innovation.....	41
C.	Likely Competition Effects of a Branded Exclusivity Period.....	42
1.	The Innovation Benefits of FOB Competition.....	42
2.	Actual Pioneer Drug Manufacturer Exclusivity Can Inform the Length of a Branded Exclusivity Period.....	42

3.	FOB Entry is Unlikely to Occur Immediately Upon Expiration of a Limited Period of Branded Exclusivity.....	43
4.	Exclusivity Periods Have Been Used When Patent Protection Has Been Insufficient to Incentivize and Reward Innovation.....	44
D.	The Nature Model Fails to Inform Reliably the Length of a Branded Exclusivity Period.....	45
CHAPTER 3	COMPETITIVE EFFECTS OF A PRE-APPROVAL PATENT RESOLUTION PROCESS.....	47
I.	INTRODUCTION.....	47
II.	THE LIKELY EFFECTS OF AN FOB PRE-APPROVAL PATENT RESOLUTION PROCESS.....	49
A.	Background on the Hatch-Waxman Pre-Approval Patent Resolution Process.....	49
B.	Commenters' and Panelists' Views on the Likely Effects of an FOB Pre-Approval Patent Resolution Process.....	50
C.	Analysis of the Likely Effects of a Pre-Approval Patent Resolution Process.....	52
1.	The Likely Market Impact of FOB Drug Entry Does Not Warrant a Special Pre-Approval Patent Resolution Process.....	52
2.	A Pre-Approval Patent Resolution Process is Unlikely to Provide Certainty and is Likely to Disrupt Innovation Incentives.....	54
3.	A Pre-Approval Process is Unlikely to be Workable and is Likely to Cause Harm.....	55
a.	Notice Provisions are Unnecessary and Could Raise Anticompetitive Concerns.....	56
(1).	Patents Claiming the Pioneer Drug Product are Publically Available.....	56

	(2). Notice of the FOB's Application Raises Competitive Concerns.....	57
b.	Identification of a Subset of Patents to Resolve During the Pre-Approval Patent Resolution Process Defeats the Purpose of a Pre-Approval Resolution Process.....	59
c.	Enforcement Provisions May Harm Innovation and Competition.....	60
CHAPTER 4	LIKELY COMPETITIVE EFFECTS OF A MARKET EXCLUSIVITY PERIOD FOR FOLLOW-ON BIOLOGICS.....	65
I.	NECESSITY OF AN EXCLUSIVITY PERIOD TO ENCOURAGE DEVELOPMENT OF FOLLOW-ON BIOLOGICS.....	66
II.	MARKETING EXCLUSIVITY LIMITED TO INTERCHANGEABLE FOLLOW-ON BIOLOGICS.....	68
III.	ANALYSIS OF LIKELY COMPETITIVE EFFECTS OF AN FOB EXCLUSIVITY PERIOD.....	69
APPENDIX A		
APPENDIX B		
APPENDIX C		
APPENDIX D		

INTRODUCTION

The Commission initiated this inquiry because decisions of regulatory bodies such as the Food and Drug Administration substantially shape business rivalry.¹ This inquiry is very mindful of how innovation in the biotechnology industry is highly dependent on patent protection.²

Biotechnology innovation is costly and unpredictable, requiring significant amounts of investment to test and commercialize new drug products. By preventing rival firms from free riding on discoveries, patents allow firms to recoup the substantial capital investments made to discover, test, and obtain regulatory approval of new drug products. Patents also are necessary to attract the capital to fund high-risk investment in the biotechnology industry.³ Thus, this report approaches this problem by examining the likely competitive effects of a new regulatory scheme in the highly risky, costly and time-consuming process of bringing new biologic drugs to the market.

Chapter 1 of this report examines the likely market impact of FOB entry and contrasts it to the market impact of small-molecule generic drugs. The Commission is mindful that the likely competitive effects of FOB entry are based on the available knowledge of existing external market conditions. For example, the likely competitive effects of FOB competition could change if technology breakthroughs occur, biosimilar safety issues arise, health insurance coverage expands, or payor and reimbursement strategies change, among others. In sophisticated industries such as biotechnology, external conditions can and do change and often alter expectations of profit-maximizing firms.⁴ This industry, however, has shown significant ability to adapt and thrive under new market conditions.⁵ The Commission expects the robust and dynamic market conditions of the biologic drug industry to continue with the entry of FOB drug products.

Chapter 2 examines whether in addition to patent protection and market-based pricing, pioneer biologic drug products need a branded exclusivity period to promote innovation in biologic drug markets. Chapter 3 examines whether special procedures are necessary to resolve

¹ The Commission outlined its preliminary views on the likely effects of an abbreviated regulatory approval pathway for biologic drug products in May 2008. See Letter of the Federal Trade Commission to the Honorable Frank Pallone, Jr., Chairman, Subcommittee on Health, Committee on Energy and Commerce, House of Representatives (May 2, 2008), available at: http://energycommerce.house.gov/Press_110/110-ltr.050208.respto040308.FTC.pdf.

² It is beyond the scope of this report to determine whether a 20-year patent life is the optimal period to incentivize innovation in this and other industries that rely on patent protection.

³ See FEDERAL TRADE COMM'N, TO PROMOTE INNOVATION: THE PROPER BALANCE OF COMPETITION AND PATENT LAW AND POLICY (2003), Ch. 3 at 1, available at <http://www.ftc.gov/os/2003/10/innovationrpt.pdf>.

⁴ See Charles E. Phelps, *Managing the Market: Regulation and Technical Change in Health Care*, HEALTH ECONOMICS, at 498-546 (3rd ed. 2003).

⁵ See Iain M. Cockburn, *The Changing Structure of the Pharmaceutical Industry*, 23 HEALTH AFFAIRS 1:10-22, 14 (2004).

potential patent disputes between pioneer and FOB manufacturers prior to FDA approval of an FOB drug product. Chapter 4 examines whether market profits are insufficient to incentivize the development of interchangeable FOB products.

The FTC appreciates the 29 comment filers and 30 panelists who contributed time, effort, and thoughtful analysis to these issues before, during, and after the public roundtable discussion. We also are grateful for the intellectual property and economic experts proffered by the biotechnology and pharmaceutical manufacturers.

CHAPTER 1 BACKGROUND AND LIKELY MARKET IMPACT OF FOLLOW-ON BIOLOGIC COMPETITION

I. BACKGROUND

Innovations in biotechnology have improved medical treatments, reduced suffering, and saved the lives of millions of Americans. The lure of patent protection, coupled with the ability to price at market rates, has spurred pioneer drug manufacturers to develop new therapeutic drugs known as biologics.¹ The Food and Drug Administration (“FDA”) approves biologic drugs under the Public Health Safety Act (“PHS Act”).

These innovations, however, are expensive. As examples, annual treatment for breast cancer with the biologic drug Herceptin can cost \$48,000 and the annual treatment for rheumatoid arthritis with Remicade can cost approximately \$20,000. Indeed, in 2007, Americans spent \$286.5 billion for prescription drugs, \$40.3 billion of which was for biologic drugs.²

In 1984, Congress enacted the Hatch-Waxman Act to allow the FDA to approve the sale of generic or follow-on versions of off-patent branded drugs.³ This process applies to drugs regulated only under the Federal Food Drug and Cosmetic Act (“FD&C Act”), which are generally chemically-synthesized, small-molecule products. It does not apply to drugs approved under the PHS Act.

Under Hatch-Waxman, generic applicants are not required to duplicate the clinical testing of drugs already proven safe and effective. Rather, to be approved, the applicant must show that its generic drug product is the same as the branded drug product. A bioequivalence showing is much less expensive than the clinical testing required for a pioneer branded drug product and thus, is an efficient way to leverage scarce research and development (“R&D”) funds to target innovative drug development.

¹ Biologic drugs are derived from living matter or manufactured in living cells using recombinant DNA biotechnologies. See FDA Center for Biologic Drug Evaluation and Research (CBER), *Frequently Asked Questions About Therapeutic Biologic Drug Products*, available at <http://www.fda.gov/cder/biologics/qa.htm>.

² These sales figures are based on wholesale prices reported in the IMS Top Line Industry Data. Press Release, IMS Health, IMS Health Reports U.S. Prescription Sales Jump 3.8 Percent in 2007, to \$286.5 Billion (March 12, 2008), available at <http://www.imshealth.com> (follow “Press Room” hyperlink; then follow “IMS Health Care Reports News Release” hyperlink); see also CONG. BUDGET OFFICE (“CBO”) 110TH Cong., BUDGET OPTIONS VOL.1: HEALTH CARE at 126-28 (2008), available at <http://cbo.gov/ftpdocs/99xx/doc9925/12-18-HealthOptions.pdf> [hereinafter, “BUDGET OPTIONS”].

³ See The Federal Food, Drug, and Cosmetic Act, 21 U.S.C.A. § 301, *et seq.* (2009), as amended by The Drug Price Competition and Patent Term Restoration Act of 1984 [hereinafter, the “Hatch-Waxman Act” or “Hatch-Waxman”] and the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, 21 U.S.C.A. § 355(j) (2009) and 35 U.S.C.A. § 271(e) (2009). See Appendix B for a description of the new and abbreviated drug approval processes.

Competition provided by the generic drug industry has reduced prescription drug prices, increased access for more Americans, and hastened the pace of innovation.⁴

There is no similar approval process for biologic drugs.⁵ Rather, once a biologic drug product's patents expire, the follow-on applicant must duplicate the clinical testing of the pioneer biologic drug. This duplication of safety and efficacy information is costly, an inefficient use of scarce resources, and, as the FDA has explained, raises ethical concerns associated with unnecessary human testing.

The desire to avoid these consequences by creating an approval process for follow-on biologic ("FOB") drugs takes on urgency in light of the significant number of biologic drugs that go off-patent within the next several years. Figure 1-1 shows the 27 top selling biologic drug products, many of which go off patent by 2015.⁶ The drugs listed comprise approximately 87 percent of the total global value of the biologics industry of \$112 billion.

⁴ See generally Jennifer S. Haas et al., *Potential Savings from Substituting Generic Drugs for Brand-Name Drugs: Medical Expenditure Panel Survey, 1997-2000*, 142 ANNALS INTERNAL MED. 891 (June 2005); Wendy H. Schacht & John R. Thomas, Congressional Research Service (CRS), Library of Congress, *Report for Congress, Follow-On Biologics: Intellectual Property and Innovation Issues*, at 4 & 18, 110th Cong. (Jan. 17, 2008), available at http://www.biosimilars.com/CRS_FOBs.pdf.

⁵ See *Assessing the Impact of a Safe and Equitable Biosimilar Policy in the United States Hearing Before H. Subcomm. on Health and the H. Comm. on Energy and Commerce*, 110th Cong. (2007) (statement of Janet Woodcock, Deputy Comm'r, Chief Medical Officer, FDA), available at http://energycommerce.house.gov/cmte_mtgs/110-he-hrg.050207.Woodcock-testimony.pdf [hereinafter, "Woodcock Statement"]. Historically, some biologic protein products have been regulated as drugs under the FD&C Act. The FDA has approved six follow-on protein products under the FD&C Act, including Hylenex (hyaluronidase recombinant human), Hydase (hyaluronidase), Fortical (calcitonin salmon recombinant) Nasal Spray, Amphadase (hyaluronidase), GlucaGen (glucagon recombinant for injection), and Omnitrope (somatropin [rDNA origin]). *Id.*

⁶ See Bernstein Research Comment (9/29/08) at 2; Biotechnology Industry Organization ("BIO"), Health Overview, available at <http://www.bio.org/healthcare> (last accessed June 8, 2009); CBO, BUDGET OPTIONS at 126; Hospira (Wilkie Farr) Comment (12/22/08) at 5 and Attachment 1. Patent expiration information was obtained from SEC form 10-K filings. FDA maintains a searchable catalog of approved drug products including drug approval history. See, Drugs@FDA, available at <http://www.accessdata.fda.gov/Scripts/cder/DrugsatFDA>.

Figure 1-1: Top-Selling Biologic Products (2008 sales in billions)

Drug	2008 Sales	Year Approved	Drug	2008 Sales	Year Approved	Drug	2008 Sales	Year Approved
Avastin	\$9.2	2004	Novolog	\$3.7	2000	Rebif	\$1.7	2002
Enbrel	\$8.0	1998	Erbitux	\$3.6	2004	Cerezyme	\$1.5	1994
Remicade	\$7.9	1998	Aranesp	\$3.2	2001	Tysabri	\$1.4	2004
Humira	\$7.3	2002	Recombinant	\$2.9	1998	NovoSeven	\$1.4	1999
Rituxan	\$7.3	1997	Lucentis	\$2.7	2006	Synagis	\$1.3	1998
Herceptin	\$5.7	1998	Avonex	\$2.6	1996	Neupogen	\$1.3	1991
Lantus	\$5.1	2000	Novolin	\$2.5	1991	Betaseron	\$1.2	1993
Epogen/Procrit	\$5.1	1989	Humalog	\$2.2	1996	Humulin	\$1.1	1992
Neulasta	\$4.2	2002	PEGASYS	\$2.0	2002	Kogenate FS	\$1.1	1993

The scientific differences between biologic and small-molecule drug products, however, complicate efforts to devise an approval process for FOB drugs. Biologic products are more complex and immunogenic than small-molecule drugs.⁷ Current technology does not yet allow for the creation of an exact replica of a pioneer biologic drug product, according to the FDA.⁸ In addition, technology is not yet robust enough to determine whether an FOB product is “interchangeable” with the pioneer product such that a patient would be able to switch between the two products without an adverse effect.

In light of these complexities, current legislative proposals permit FDA approval of an FOB drug that is sufficiently *similar* to, but not an exact replica of, the referenced branded biologic product.⁹ A showing of similarity is likely to save clinical testing expenses but would require substantially more expense than a showing of bioequivalence for small-molecule generic drugs. Unlike small-molecule drugs, FOB products would not be designated as “therapeutically equivalent” with the referenced product. The lack of therapeutic equivalence means that a pharmacist may not substitute prescriptions for a pioneer product to an FOB product without physician consent. As technology and scientific understanding develops, however, the approval process could provide a means by which an FOB applicant could show that its product is interchangeable with the pioneer product.

⁷ Immunogenicity raises safety concerns because of a biologic drug’s ability to stimulate an immune response. An immune response to a therapeutic protein can range from development of detectable but not clinically significant antibodies to an immune response with significant impact on safety or effectiveness, including the potential to decrease or block the clinical effect of the therapeutic protein. See Letter from Frank M. Torti, Principal Deputy Comm’r and Chief Scientist, FDA, to Frank Pallone, Jr., Chmn., H. Subcomm. on Health, (Sept. 18, 2008) at 1, *available at* http://energycommerce.house.gov/Press_110/fdabiosimilarrespons20080918.pdf.

⁸ *Id.* at 4; Woodcock Statement at 1 (“[T]he idea of *sameness*, as the term is used in the generic drug approval process under the [FD&C] Act and applied to small-molecules, will not usually be appropriate for more structurally complex molecules of the type generally licensed as biological products under the [PHS] Act.”).

⁹ See H.R. 1427, 111th Cong. § 3(a) (2009); H.R. 1548, 111th Cong. § 101 (2009).

In the current legislative debate, questions have arisen over whether the same issues that prompted provisions of the Hatch-Waxman Act that restrict entry by generic competitors are likely to be present in the context of FOB competition. To answer these questions, the Commission initiated a public inquiry, including a public workshop and a series of public comments, to examine how FOB competition is likely to develop to determine whether similar entry restrictions would benefit consumers.¹⁰

This chapter describes the regulatory background necessary to understand how an FOB approval process could be used by FOB manufacturers. It then describes the likely market impact of FOB entry and contrasts it to the market impact of small-molecule generic drugs. This analysis sets the stage for the discussion in Chapters 2 through 4 of specific issues regarding how to foster FOB competition to benefit consumers.

II. THE NEW DRUG AND GENERIC APPROVAL PROCESSES

A. New Drug Approval Processes Under the FD&C Act and the PHS Act

To obtain FDA approval of a new small-molecule drug under the FD&C Act or a biologic product under the PHS Act, the manufacturer must prove that the product is safe and effective. Manufacturers must submit the following information to the FDA for approval:

- (a) pre-clinical analytical tests, pre-clinical studies and formulation studies;
- (b) an Investigational New Drug Application (“IND”) to initiate human clinical testing;
- (c) adequate and well-controlled human clinical trials to establish the safety and efficacy of the drug for its intended use;
- (d) approval and validation of commercial scale manufacturing facilities used in production of the product;
- (e) drug manufacture and analytical methods; and
- (f) proposed product packaging and labeling.¹¹

The pre-clinical phase of any new drug development typically identifies compounds (either small-molecule or protein-based) that target a particular disease or are therapeutically beneficial. Once a lead compound is isolated, the manufacturer conducts pre-clinical safety trials, as well as trials in predictive animal models to determine if the compound works as expected. This pre-clinical phase typically takes one to five years.¹²

¹⁰ See Notice of Public Workshops and Roundtables and Opportunity for Comment, Emerging Health Care Competition and Consumer Issues, 73 Fed. Reg. 51479-51482 (Sept. 3, 2008), available at <http://www.ftc.gov/bc/workshops/hcbio/index.shtml>.

¹¹ See 42 U.S.C.A. § 262; 21 U.S.C.A. § 321, *et seq.* (2009).

¹² See, e.g., Ernst R. Berndt *et al.*, *Opportunities for Improving the Drug Development Process: Results from a Survey of Industry and the FDA* (Nat’l Bureau of Econ. Research, Working Paper No. W11425, 2005).

After pre-clinical tests are completed, a drug sponsor submits these results in an IND to the FDA before human clinical trials may commence.¹³

Clinical trials typically consist of three phases. In Phase I, a small group of patients is given the drug to determine if the drug is safe in humans. In Phase II, a small sample of the intended patient population is given doses of the drug to provide a preliminary assessment of the efficacy of the drug for a specific clinical indication, find dose tolerance, and find the optimal dose range. Phase III studies are initiated if Phase I and Phase II studies indicate the drug is safe and has some efficacy in the targeted patient population. Phase III studies are designed to gather sufficient data in a broad target population in order to establish safety and efficacy for a particular indication.

The time to conduct these trials varies based on factors such as indication, availability of reliable ways to measure efficacy, size of patient populations in the clinical trials, ease of patient accrual, as well as a host of other factors. Despite these variances, Phase I takes approximately one year, Phase II (including dose ranging studies) takes approximately two years, and Phase III takes approximately three years.¹⁴

B. Generic Drug Approval Under the FD&C Act

Rather than requiring a generic manufacturer to repeat the costly and time-consuming new drug approval process, the Hatch-Waxman Act permits generic drug applicants to file an Abbreviated New Drug Application (“ANDA”). The object of the ANDA process is to demonstrate that the generic drug product has the same active ingredient, route of administration, dosage form, strength, and proposed labeling as the branded drug. The ANDA also must contain sufficient information to demonstrate that the generic drug is “bioequivalent” to the relevant branded product.¹⁵ As a result of providing this information, the generic applicant may rely on the FDA’s previous findings of safety and effectiveness for the branded drug, and the applicant, therefore, does not have to perform its own clinical studies. This reliance allows generic applicants to save substantial time and development costs.¹⁶ The FDA will deem a generic drug product therapeutically equivalent to the branded product. This designation allows the generic drug to be automatically substituted by a pharmacist for the branded product.

¹³ 42 U.S.C.A. § 262; 21 U.S.C.A. § 321, *et seq.*; 21 C.F.R. 601.2; 21 C.F.R. 312 (2009).

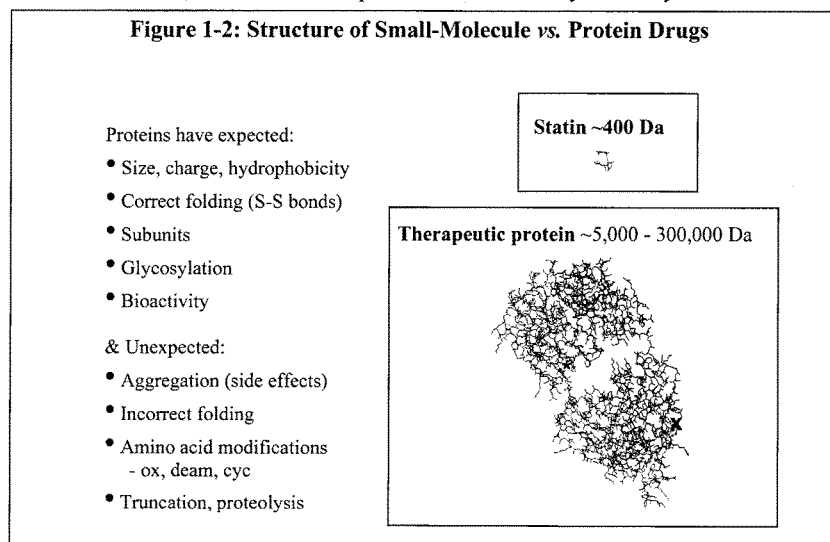
¹⁴ See Henry Grabowski *et al.*, The Effect on Federal Spending of Legislation Creating a Regulatory Framework for Public Health Service Act Follow-on Biologics: Key Issues and Assumptions, White Paper (July 1, 2007) at 8, 25, 27-28, 33 (unpublished paper on file with Analysis Group, Inc.), available at http://www.analysisgroup.com/analysisgroup/News_Study-Effects-Federal-Spending-Follow-On-Biologics-Legislation.aspx [hereinafter “White Paper”].

¹⁵ 21 U.S.C.A. § 355(j)(2)(A)(iv)(2009). Bioequivalence means that the rate and extent of absorption of the generic drug is not significantly different from the rate and extent of absorption of the reference listed drug when administered at the same dosage.

¹⁶ CBO, *How Increased Competition from Generic Drugs Has Affected Prices and Returns in the Pharmaceutical Industry*, at ix (1998), available at <http://www.cbo.gov/ftpdocs/6xx/doc655/pharm.pdf> [hereinafter, “*Increased Competition from Generic Drugs*”].

C. Issues in Translating the Generic Drug Approval Process to Biologic Drugs Under the PHS Act

The scientific differences between biologic and small-molecule drugs complicate efforts to devise an approval process for FOB drugs based on bioequivalence.¹⁷ Figure 1-2 shows the size differences between a typical small-molecule drug and a biologic protein and lists some of the complexities surrounding protein drugs. These differences include a ten to hundred-fold difference in size. A small-molecule drug, such as a statin (*e.g.*, Lipitor, Mevacor), is small (only 400 Daltons) and simple in contrast to a biologic drug. A biologic drug is significantly larger (5,000-300,000 Daltons) and has a complex structure with three-dimensional folding which performs complex binding, unlike small-molecules. Any deviation in a biologic protein's structure can result in aggregation, incorrect folding and structural anomalies (*e.g.*, truncation, proteolysis and amino acid modifications) that can have unexpected effects on efficacy and safety.¹⁸



Source: Behrman Presentation at 6

¹⁷ Testimony of Rachel Behrman, Associate Comm'r for Clinical Programs, Director of the Office of Critical Path Programs, FDA, at FTC Roundtable: Emerging Healthcare Competition and Consumer Issues (Nov. 21, 2008) at 10-20, available at <http://www.ftc.gov/bc/workshops/hcbio/transcripts/081121biologic-transcript.pdf> [hereinafter transcript cites are referenced as [last name] at [page]]; Woodcock Statement at 8-9.

¹⁸ Behrman at 10-20; Rachel Behrman, *Follow-on Biologics: A Brief Overview at FTC Roundtable: Emerging Healthcare Competition and Consumer Issues* (Nov. 21, 2008) at 6 [hereinafter "Behrman Presentation"].

Current limitations in analytical methods make it difficult to characterize and compare large molecules to determine their level of sameness. Manufacturing a consistent biologic drug product presents additional difficulties.¹⁹ In light of these challenges, it is unlikely that FOB manufacturers could only use analytic methods to show that their FOB products have the same active ingredient as the pioneer biologic product, as generic small-molecule drug applicants do pursuant to the Hatch-Waxman Act.²⁰

In light of these complexities, current legislative proposals permit FDA approval of an FOB drug that is sufficiently *similar to*, but not an exact replica of, the pioneer product.²¹ A showing of similarity is likely to save clinical testing expenses but would require substantially more expense than a showing of bioequivalence for small-molecule generic drugs. The amount of savings, however, may vary depending upon the complexity of the pioneer product to ensure that the FOB product is safe, pure and potent.²² Although abbreviated compared to a full development program, FOB applicants are likely to perform Phase I and Phase III studies, but with fewer patients. FOB manufacturers also must seek approval and validation of their commercial-scale manufacturing facilities at or before initiation of clinical trials.²³ For each additional indication for which they seek labeling, FOB manufacturers are likely to be required to perform Phase I – Phase III clinical testing.²⁴

¹⁹ See Woodcock Statement at 8 (“Because of the variability and complexity of protein molecules, current limitations of analytical methods, and the difficulties in manufacturing a consistent product, it is unlikely that, for most proteins, a manufacturer of a follow-on protein product could demonstrate that its product is identical to an already approved product.”); Behrman Presentation at 6; Behrman at 13-20.

²⁰ See Behrman at 12-13 (“[P]roteins [biologics] . . . are chains of amino acids . . . they can range from very simple to extremely complex, and when they're very complex, they are folded; they have things stuck on them; they can unfold again; and then they can aggregate.”); see also Norman at 153 (“[T]he chemical [small-molecule] compound itself is something that always looks like chicken wire, so it's got a methyl on one end and maybe an ethyl on the other, but it's going to look like methyl ethyl chicken wire, and every follow-on generic or branded firm] that makes that molecule . . . is going to make methyl ethyl.”).

²¹ See S. 1695, 110th Cong. (2008); H.R. 1427, 111th Cong. (2009).

²² See Woodcock Statement at 11 (“When the mechanism of action is well understood and there is a significant amount of clinical experience with a product, it may be easier to make a scientific assessment of the ability to rely on conclusions about safety and efficacy from a prior application.”).

²³ For a description of the FDA clinical requirements required to approve the first biosimilar product in the U.S. see Letter from Director Steven K. Glason, Center for Evaluation and Research (“CDER”), FDA to Petitioners (May 30, 2006) at 7, 25 (Novartis’ application for Omnitrope included “CMC[chemistry, manufacturing and control], nonclinical pharmacology and toxicology, human pharmacokinetic and pharmacodynamic, and clinical safety and effectiveness data,” including 3 Phase III trials), *available at* <http://www.fda.gov/ohrms/dockets/dockets/04P0231/04P-0231-pdn0001.pdf> [hereinafter “FDA’s Second Response to Omnitrope CPs”]; see Grabowski, *White Paper* at 25-26 (“Obtaining approvable [FOB] manufacturing capacity may take 3 to 7 years.”).

²⁴ See Henry Grabowski *et al.*, *Entry and Competition in Generic Biologics*, 28 MANAGERIAL AND DECISION ECONOMICS 439-51 (development time for FOB estimated at 5-8 years, 3 years for preclinical

Unlike small-molecule drugs, FOB products would not be designated as “therapeutically equivalent” with the referenced product. The lack of therapeutic equivalence means that a pharmacist may not substitute prescriptions for a pioneer product to an FOB product without physician consent. The approval process could provide, however, a means by which an FOB applicant could show that its product is interchangeable with the pioneer product as technology and scientific understanding develops.²⁵

It also is likely that FOB manufacturers could become innovators. For example, they may develop “biobetter” FOB drugs that improve upon the safety and effectiveness of the pioneer product. In other instances, FOB firms could develop improved manufacturing processes and analytics, resulting in safer biologics manufactured by both pioneer and FOB manufacturers, and/or more efficient manufacturing and testing methodologies, resulting in lower-priced biologic drugs.²⁶ One commenter suggested that the “incentive for enhanced and innovative biologics manufacturing capacity is an oft-forgotten but critically-important aspect of innovation, particularly in the context of biologics, and it is one that can enable a direct reduction in the cost of goods and an increased durability of supply.”²⁷

III. PHARMACEUTICAL PRICING, MARKET DYNAMICS AND THE LIKELY COMPETITIVE IMPACT OF FOLLOW-ON BIOLOGICS

Pioneer manufacturers, potential FOB manufacturers, and payors explained that it is likely that an FOB approval process under the PHS Act will result in the approval of biosimilar products, not interchangeable ones. This section describes the likely market

work, 2-4 years for clinical trials and 1 year for FDA approval); Grabowski, *White Paper* at 25-26 (“FOB development and trials will likely take 3 to 5 years, and obtaining FDA approval another one and a half to two years.”); *see also id.* at 5, 27-30.

²⁵ The term “interchangeable” is not currently defined in the PHS Act. Many panelists and commenters suggested that interchangeability was unlikely to be possible in the near term. *See* Buckley at 47 (“In Europe, to date 14 countries have ruled that these products are not interchangeable”); *see id.* at 51; Phillips at 103. Participants noted that the European Union (“EU”) member states (including France, Germany, United Kingdom, Italy and Spain) have all rejected the practice of substitution of a biologic by the pharmacist without the physician’s consent. Amgen Comment (9/30/08) at 2-3, 6; Novartis Comment (9/29/08) at 2, 16-17; Brugger at 38-39.

²⁶ *See* Behrman at 78; *see also* Momenta Comment (12/22/2008) at 3 (new analytic tools developed by Momenta to characterize proteins may provide significant “value and cost savings to the innovator drug development process . . . to enhance the quality of their products by more precisely controlling variability of a number of attributes in the final drug product . . . and reduce the need for very costly, potentially unnecessary clinical trials.”).

²⁷ Novartis Comment (9/29/08) at 3-4; Brugger at 54 (“We’ve developed an innovative analytical approach to these complex molecules, both in better understanding the [biologic] product, but also a deeper understanding of the manufacturing process.”); *see also id.* at 55, 79; Momenta Comment (9/30/08) at 2.

effects of biosimilar product entry and contrasts it to the market effects of entry by small-molecule generic drugs.

A. Pharmaceutical Pricing and the Effect of Generic Drug Entry

In the United States, a pioneer manufacturer of either small-molecule or biologic drugs is free to charge a monopoly price for its product to the extent the market conditions permit or it is perceived to offer greater health benefits compared to existing drugs or medical treatments.²⁸ Patent-protected drug products also may be able to prevent the manufacturer from facing competition, thus enabling the manufacturer to charge a monopoly price.

Manufacturers of small-molecule and biologic drugs market their products through a variety of channels including a specialty detail sales force, free samples or prescription coupons, medical education and conferences, peer review journal publications, direct-to-consumer advertising, and formulary access. Formulary access is controlled either by private prescription benefit managers (“PBMs”) for reimbursement by health insurance companies or managers for coverage by various public payors (*e.g.*, Department of Veterans Affairs, Medicare, state Medicaid programs).²⁹

Approval of a breakthrough or pioneer drug product is increasingly followed by entry of a subsequent branded product(s).³⁰ The head start that the breakthrough product has had over subsequent branded products has decreased over the past three decades from 8.2 years during the 1970s to 2.25 years in the 1990s.³¹

²⁸ See FEDERAL TRADE COMM’N, PHARMACY BENEFITS MANAGERS: OWNERSHIP OF MAIL ORDER PHARMACIES, (August 2005) [hereinafter “FTC PBM REPORT”] at 63, available at <http://www.ftc.gov/reports/pharmbenefit05/050906pharmbenefitrpt.pdf>.

²⁹ Generally, each PBM negotiates with branded drug manufacturers for discounts or market share payments that are based on the branded drug’s preferred status on the PBM’s drug formulary or on the branded drug’s market share among the PBM’s members. Branded drug manufacturers make these payments to encourage the PBM to dispense their branded drugs rather than competing branded products within a therapeutic class. Drug formularies are used primarily for drugs dispensed in a retail pharmacy environment. See FTC PBM REPORT, Ch. 1 at 4, 6.

³⁰ Joseph A. DiMasi & Cherie Paquette, *The Economics of Follow-on Drug Research and Development*, 22 PHARMACOECONOMICS Supp 2:1-14 (2004) (The study included several biologic drugs). In the 1990s all of the breakthrough products had branded competitors in clinical development at or before their approval; *id.* at 10.

³¹ *Id.*; F.M. Scherer, *Markets and Uncertainty in Pharmaceutical Development* 13 (FACULTY RESEARCH WORKING PAPERS SER., HARV. UNIV., JOHN F. KENNEDY SCHOOL OF GOV’T, 2007), available at [http://ksgnotes1.harvard.edu/Research/wpaper.nsf/rwp/RWP07-039/\\$File/rwp_07_039_scherer.pdf](http://ksgnotes1.harvard.edu/Research/wpaper.nsf/rwp/RWP07-039/$File/rwp_07_039_scherer.pdf).

When the FDA approves a branded competitor, price competition ensues, market size expands, and market share shifts among the competitors.³² Brand-to-brand competition results in negotiated price discounts in the range of 18 to 27 percent off the pioneer's product price.³³ Brand-to-brand competition also expands the market (in units and dollars) for a therapeutic class of drugs by increasing awareness of conditions and treatments from increased detailing, advertising, and marketing, as firms compete to influence physician prescribing behavior in favor of their brands.³⁴ Price competition among branded firms therefore increases access for patients.

For drugs approved under the FD&C Act, generic entry occurs when patent protection ends³⁵ (either at patent expiration or by a court finding of non-infringement or invalidity). The number of generic entrants after patent expiration is largely a function of fixed entry costs compared to the market opportunity.³⁶ The first generic entrant generally offers a price that is 25 percent lower than the branded drug's price. The price discount can rise to 80 percent with multiple generic entrants.³⁷

³² See FEDERAL TRADE COMM'N, TO PROMOTE INNOVATION: THE PROPER BALANCE OF COMPETITION AND PATENT LAW AND POLICY (2003), Ch. 2 at 11 [hereinafter "FTC PATENT REPORT"], available at <http://www.ftc.gov/os/2003/10/innovationrpt.pdf>; FTC/DOJ HEALTH CARE REPORT, Ch. 6 at 3-9.

³³ Although the competing branded product's list price, including Average Wholesale Price ("AWP") or Wholesale Acquisition Cost ("WAC"), is typically at parity, the firms compete by offering price discounts to the largest, most sophisticated, and price sensitive customers, such as PBMs. These discounts are confidential. See IMPROVING HEALTH CARE: A DOSE OF COMPETITION: A REPORT BY THE FEDERAL TRADE COMM'N AND THE DEP'T OF JUSTICE (July 2004), Ch. 7, at 11-17, available at <http://www.ftc.gov/reports/healthcare/040723healthcarerpt.pdf> [hereinafter "FTC/DOJ HEALTH CARE REPORT"]; see also DiMasi and Paquette, *The Economics of Follow-on Drug Research and Development*, at 12 (average discount offered by subsequent branded rivals were 26% off price leader and 14% off the class average); CBO, *Increased Competition from Generic Drugs*, at 24-25.

³⁴ See FTC/DOJ HEALTH CARE REPORT, Ch. 6-7; FTC PATENT REPORT, Ch. 2, at 11.

³⁵ In general, if the patent application was filed after June 7, 1995, the patent expires 20 years from the date on which the application was filed. 35 U.S.C.A. § 154(a)(2)-(3) (2009). If the application was filed by June 7, 1995 and issued after June 7, 1978, the term is the later of 17 years from issuance or 20 years from filing. 35 U.S.C.A. § 154(c). If the application was filed by June 7, 1995 and issued before June 8, 1978, the expiration date was 17 years from issuance, i.e., 1995 or earlier.

³⁶ Generally, the number of generic entrants increases with the market size. In one study of the 40 oral small-molecule drugs with patent expiry between 1992 to 1998, an average of 12 generic firms entered when the market size before patent expiry was over \$250 million. In comparison, when market size was less than \$250 million, only 5 generic firms entered. Grabowski, *Entry and Competition*, at 440, 444-46; see also David Reiffen & Michael R. Ward, *Generic Drug Industry Dynamics*, 87 REVIEW OF ECONOMICS AND STATISTICS, 37-49, 38 (2005) ("more firms enter, and enter more quickly, in markets with greater expected rents"), available at <http://www.ftc.gov/be/econwork.htm>.

³⁷ See Reiffen, *Generic Drug Industry Dynamics*; see also CBO, *Increased Competition from Generic Drugs*, at 28; Grabowski, *Entry and Competition*, at 444, 446 (economic analysis concludes that 1 generic entrant results in discounts of 10%, 5 generic firms 37%, 5 entrants 40%, 10 entrants 60%, and 95% after 20 entrants); Grabowski, *White Paper* at 42-44, 52-53; OTA, *Pharmaceutical R&D*, at 297; Roy Levy, *THE PHARMACEUTICAL INDUSTRY: A DISCUSSION OF COMPETITIVE AND ANTITRUST ISSUES IN AN ENVIRONMENT OF CHANGE* (1999) at 73-76, 197 [hereinafter "LEVY REPORT"], available at <http://www.ftc.gov/os/2006/07/P052103BarrierstoGenericEntryTestimonySenate07202006.pdf>.

Marketplace experiences have documented the rapid erosion of a branded drug's sales once the first generic product is introduced.³⁸ The rapid decline of the branded product's market share is largely a function of state substitution laws and price sensitive customers' use of drug formularies.³⁹ State substitution laws allow a pharmacist to dispense a generic drug when presented with a prescription for its branded equivalent, unless the physician or consumer directs otherwise. In addition, PBMs and retail pharmacies have substantial incentive to dispense generic drugs because the margins on generic drugs are greater than they are for branded products, resulting in greater profits for PBMs and retail pharmacies.⁴⁰ These two factors enable the generic entrant to erode a majority of the market share of the branded product within the first year.⁴¹ When additional generic firms enter, they compete against incumbent generic firms for market share, not the branded manufacturer, because the first generic firm has already obtained most of the branded manufacturer's sales.

B. Likely Market Effects of Biosimilar Entry

Competition from FOB drug entry is likely to resemble brand-to-brand competition rather than generic drug competition.⁴² Experience to date for two products

³⁸ See Grabowski at 42 (generic erosion 90%), Heldman at 26-28 (generic erosion 80%); see also Golding at 49, Buckley at 52; Grabowski, *Entry and Competition*, at 444 (brands lose 67% of market share within a year); CBO, *Increased Competition from Generic Drugs* at 29-31; David Reiffen & Michael Ward, "Branded Generics" *As A Strategy To Limit Cannibalization of Pharmaceutical Markets*, 28 *MANAGERIAL AND DECISION ECONOMICS*, 251-65 (2005), available at http://fda.gov/oc/healthcare/wp/12_Reiffen_BrandedGenericsAsAStrategy.pdf; Henry Grabowski & John Vernon, *Longer Patents for Increased Generic Competition in the U.S.: The Hatch-Waxman Act After One Decade*, 10 *PHARMACOECONOMICS* supp. 2:110-23 (1996) (brands lost 50% of prescriptions within a year); U.S. Cong., Office of Technology Assessment ("OTA"), *Pharmaceutical R&D: Costs, Risks and Rewards*, OTA-H-522 (1993), at Table F-3, p. 297, available at <http://www.princeton.edu/~ota> (Princeton University hosts the OTA legacy site, follow "OTA publications" hyperlink and use search engine there to find article by title) [hereinafter "Pharmaceutical R&D"].

³⁹ See CBO, *Research and Development in the Pharmaceutical Industry* at 48 (2006), available at <http://www.cbo.gov/ftpdocs/76xx/doc7615/10-02-DrugR-D.pdf>; CBO, *Increased Competition from Generic Drugs*, at 27-30; Grabowski, *Entry and Competition*, at 444-45.

⁴⁰ See FTC PBM REPORT at x, 12, 74-75.

⁴¹ See Reiffen & Ward, *Branded Generics*; Grabowski & Vernon, *Longer Patents for Increased Generic Competition*; Grabowski, *Entry and Competition*, at 444.

⁴² See Duke University Comment (12/23/08) at Table 3; BIO Comment (9/30/08) at 2; Grabowski *White Paper* at 2, 4-6, 8-9, 40-41, 48; see also Paul Heldman *et al.*, Citigroup Research, Citigroup Global Markets, *A Global "Generic Biologics" Guidebook* at 5 (November 6, 2006) [hereinafter "Citigroup 2006 FOB Guidebook"]; *Safe and Affordable Generic Biotech Drugs: The Need for a Generic Pathway: Hearing before the H. Oversight and Gov't Reform Comm.*, 110th Cong. 1-14 (2007) (statement of Henry Grabowski, Duke University), available at <http://oversight.house.gov/documents/20070416132526.pdf>; Grabowski, *Entry and Competition*, at 448-49 (after extensive economic modeling, the authors conclude that and FOB prices relatively close in price to branded biologics); CBO Cost Estimate (S.1695), *Biologics Price Competition and Innovation Act of 2007 S. 1695, As Ordered Reported by the S. Comm. on Health,*

with both branded and FOB competitors (in Europe and the U.S.) shows that four factors have dampened substantial price discounting by, and rapid share shifting to, FOB manufacturers as compared to the effects of generic drug entry. As a result, branded manufacturers are likely to continue to reap profits after FOB entry.

1. Fewer FOB Competitors Due to High Barriers to Entry

Fewer FOB competitors are expected due to the technological barriers and the high cost of entry.⁴³ FOB products are likely to take eight to 10 years to develop and to cost between \$100 and \$200 million.⁴⁴ Higher development costs for FOB products, compared to small-molecule generic drugs, include those associated with manufacturing, clinical trials, and post-marketing surveillance.⁴⁵ By contrast, small-molecule generic drugs product development costs range from approximately \$1 to \$5 million.

Follow-on biologic manufacturers will likely have to build, equip and qualify their own manufacturing facilities, which is likely to cost \$250 to \$1 billion.⁴⁶

Education, Labor, and Pensions on June 27, 2007 (June 25, 2008), available at <http://www.cbo.gov/ftpdocs/94xx/doc9496/s1695.pdf> [hereinafter "S. 1695 Report"].

⁴³ See CBO S. 1695 Report at 6 ("CBO expects that certain drugs could face competition from several firms by 2018, although we believe it would be more typical for an innovator biologic to face competition from between one and three competitors."); Grabowski, *Entry and Competition*, at 446-47 (because of bioreactor capacity constraints and high fixed costs for *de novo* biologic manufacturing facilities, the number of FOB entrants is likely to be smaller than that predicted for generic small-molecule markets for the foreseeable future); see also Buckley at 53 ("The number of entrants will certainly be fewer. . . There are technological know-how [barriers] . . . the price of clinical trials . . . the length of the approval process, the likelihood of a successful application . . . and you start to see that the number of players that can submit a successful application is just much smaller."); Amgen Comment (9/30/08) at 5; Alhstrom at 44-45; Grabowski at 42; Heldman at 25; Lane at 46. The technological barriers to entry vary on the complexity of the biological product. Several FOB manufacturers are predicted to be able to obtain FDA approval for biosimilar versions of first generation recombinant proteins. However, as the biological products become more scientifically complex, as in the case of many of the monoclonal antibodies, the technological barriers to entry are so significant that few predict FOB in the next decade.

⁴⁴ See Sumanth Kambhammettu, Senior Research Analyst, Frost & Sullivan, *The European Biosimilars Market: Trends and Key Success Factors*, (Oct. 27, 2008) ("average cost of bringing a biosimilar to market is around \$100-\$200 million"), <http://www.obbec.com/specialreports/20-biopharmaceuticals/2152-the-european-biosimilars-market-trends-and-key-success-factors>; CBO S. 1695 Report at 6; Duke University Comment (12/23/08) at Table 3; BIO Comment (9/30/08) at 2; Grabowski *White Paper* at 2, 4-6, 8-9, 40-41, 48; Grabowski, *Entry and Competition*, at 442; Citigroup 2006 FOB Guidebook at 5; see also Ahlstrom at 53; Lane at 40, 46; Zuckerman Comment (12/22/08) at 12.

⁴⁵ See BIO Comment (9/30/08) at fn. 2, 1, 9, 17, 20; Grabowski, *White Paper*; CBO S. 1695 Report at 4-7; GPhA Comment (9/30/08) at 3 (citing CBO, *Increased Competition from Generic Drugs*).

⁴⁶ See Novartis Comment (9/29/08) at 7; Wyeth Comment (12/18/08) at 6 ("[T]he cost of manufacturing facilities is staggering, and this large investment must be made long before a product is approved by the regulatory agencies."); Henry Grabowski, *Follow-on Biologics: Data Exclusivity and the Balance Between Innovation and Competition*, 7 NATURE REVIEWS DRUG DISCOVERY 479, 483 (June 2008) [hereinafter "NATURE"]; Patent Reform Act of 2007: Hearing on H.R. 1908 Before the H. Subcomm. on Courts, the Internet, and Intellectual Property of the H. Comm. on Judiciary, 110th Cong. 65 (2007) (statement of

Additionally, biologic manufacturing is costly, difficult and often requires acquiring or duplicating proprietary cell lines that are protected by both patents and trade secrets. These barriers further reduce the number of likely successful FOB entrants.

In addition to the development and manufacturing costs, FOB competitors are likely to engage in marketing and sales support for their FOB products.⁴⁷ These high costs are likely to limit FOB drug entry to markets with sales in excess of \$250 million per year.⁴⁸

In light of these high entry costs, FOB entrants are likely to be large companies with substantial resources. Current biologic drug manufacturers are likely to become FOB competitors in those markets in which they do not currently compete. Potential FOB entrants could include well-established biotechnology, and hybrid biopharmaceutical firms such as: Abbott, AstraZeneca (acquisition of MedImmune and CAT), Baxter (acquisition of Knoll), Biogen/IDEC, Eli Lilly (acquisition of Imclone), Johnson & Johnson (acquisition of Centocor), Pfizer (recent announced acquisition agreement with Wyeth), Roche (acquisition of a majority interest in Genentech), Novo Nordisk, and Sanofi-Aventis.⁴⁹

FOB firms in Europe who have an interest in developing FOB products for the U.S. market include: Novartis (including its generics division Sandoz), Teva, Hospira (partnering with German generics firm Stada), and Momenta (partnering with Novartis). Additionally, commenters recognized branded pharmaceutical firms such as Merck, Boehringer Ingelheim, and Wyeth.⁵⁰

Kevin Sharer, Amgen, Inc. ("Amgen" CEO), available at <http://judiciary.house.gov/hearings/April2007/Sharer070426.pdf>. ("It takes approximately 5 years and \$1 billion to build a factory to produce biotech medicines."). FOB manufacturers will likely have to develop their own in-house manufacturing because the worldwide capacity constraints puts greater leverage in the hands of contract manufacturers to seek maximum profits by maintaining their relationships with branded firms and the highest revenue producing branded products. Grabowski, *Entry and Competition*, at 442.

⁴⁷ See Lane at 35-36; Urlep at 34.

⁴⁸ Janet Woodcock *et al.*, *The FDA's Assessment of Follow-On Protein Products: a Historical Perspective*, 6 NATURE REVIEWS DRUG DISCOVERY 437-42 (June 2007); Grabowski, *Entry and Competition*, at 446 (only 3 entrants predicted in markets where the branded biologic has sales over \$1 Billion).

⁴⁹ See Natasha Singer, *Bristol-Myers's Reliance on Three Drugs Casts Doubt on Strategy*, N.Y. TIMES, Jan. 27, 2009, at B3 (listing recent biopharmaceutical acquisitions); Andrew Jack, *Sanofi-Aventis Ready to Join Pfizer on the Acquisition Trail*, FINANCIAL TIMES, February 2, 2009 at 13 ("[T]he latest is a spurt of consolidation in the pharmaceuticals sector"); Andrew Pollack, *Wyeth Deal May Slow Pfizer Biotech Acquisitions*, N.Y. TIMES, JAN. 26, 2009, at B4; ("Schering-Plough's considerable biologics expertise will complement Merck's novel proprietary biologics platform"), available at http://www.merck.com/newsroom/press_releases/corporate/2009_0309.html.

⁵⁰ See CVS Caremark Comment (12/22/08) at 3; Momenta Comment (12/22/2008) at 4; Andrew Jack, *AstraZeneca Chief Calls the Shots*, FINANCIAL TIMES, December 23, 2008 at 18 ("The move is the third instance in recent weeks of a large pharmaceutical company [AstraZeneca] that has been traditionally focused on developing innovative medicines to express a desire to shift to generic [biologic] medicines."); Susan Todd, *Merck Launches Biologic Division Drugmaker to Invest \$1.5 B into Venture*, NEWARK STAR

2. Lack of Interchangeability

The lack of interchangeability and automatic FOB substitution are likely to dampen how quickly an FOB manufacturer acquires market share compared to generic drug entry.⁵¹ In small-molecule drug markets, automatic substitution erodes a branded manufacturers' market share quickly once the first generic product enters the market. As more generic products enter, they compete for market share among themselves, as the branded manufacturer already has lost its market share to the first generic entrant. This situation is unlikely to occur in FOB markets as FOB manufacturers will be required to market their products and negotiate individual contracts with purchasers in competition with the branded manufacturer's product.⁵² FOB market share is likely to depend on: order of entry into the market; clinical trial results; size of detailing sales force; direct-to-consumer advertising; and access to formularies, which include price discounts to the most sophisticated, price-sensitive customers.⁵³

FOB market penetration also is likely to be hampered by lingering or institutionalized uncertainty about interchangeability and safety differences between pioneer and FOB products.⁵⁴ This uncertainty may be heightened if the FOB product does not share the same name as the pioneer biologic product.⁵⁵ Physicians and their

LEDGER, December 10, 2008 at 61 ("We anticipate that [Merck] will take a leadership position in follow-on biologics."). Merck BioVentures is developing an FOB equivalent to Amgen's Aranesp which Merck expects to launch in 2012 to be followed by five more FOBs of several best-selling biologic drugs due to lose patent protection by 2017. On November 24, 2008, Eli Lilly and Company acquired the biologic company Imclone, the biologic manufacturer of Erbitux (with global sales of \$3.6 billion) for \$6.5 billion beating out Bristol-Myers Squibb. Press Release, Eli Lilly & Co., Lilly to Acquire Imclone Systems in \$6.5 Billion Transaction, (October 6, 2008), available at <http://newsroom.lilly.com/releasedetail.cfm?ReleaseID=338523>. In June 2007, AstraZeneca completed its \$15 billion acquisition of MedImmune. AstraZeneca, Annual Report and Form 20-F Information, at 83-84 (2007); Bernstein Research Comment (9/29/08) at 2.

⁵¹ See, e.g., CCPM Comment (9/30/08) at 3 ("In the absence of a designation as interchangeable, it likely will take longer for the [biosimilar] to garner significant market share and brand manufacturers will have less incentive to compete based on price."); see also CVS Caremark Comment (12/22/08) at 4.

⁵² See, e.g., Hospira (Wilkie Farr) Comment (12/22/08) at 5 ("Without an 'interchangeable designation, biosimilar companies would be compelled to invest significant sums to market and promote biosimilars, thus driving up the cost to the consumer. Reference companies also would have less incentive to compete on price. Reference drug companies would be more likely to try to out-market the biosimilar companies, further driving up the costs of both the reference drug and market entry by the biosimilar.").

⁵³ See *supra* notes 35-40 and accompanying text regarding negotiated price discounts for different purchasers.

⁵⁴ See Amgen Comment (9/30/08) at 2-3; BIO Comment (12/22/08); Ahlstrom at 43.

⁵⁵ Generally, the FDA approves the use of the same name for a generic small-molecule as the reference branded drug because both products share the same active ingredient. In contrast, an FOB drug manufactured by a different process than the reference branded biologic drug may share the same mechanism of action, may share the same efficacy and side effects, and may even be considered or approved as interchangeable with the reference branded biologic drug but may still not be given the same name as the brand. See Horton at 98; BIO Comment (9/30/08) at 4; PCMA Comment (9/26/2008) at 5;

patients who have been safely taking a pioneer biologic drug product may be reluctant to switch to an FOB product because of the risk that the patient will react differently to the new drug.⁵⁶ These concerns may limit the FOB market opportunities to newly diagnosed patients or patients who had not improved by using the pioneer biologic drug. These concerns may dissipate as providers become more experienced with FOBs.⁵⁷

3. Specialty Pharmaceutical Characteristics

The specialty pharmaceutical characteristics of FOB drugs also are likely to constrain market share acquisition.⁵⁸ Specialty drugs, including biologic drugs, are commonly used to treat patients with severe, chronic diseases and sometimes fatal conditions. These drugs, which are primarily injected or infused, are combined with ancillary medical services and products which require specialty training for proper handling and administration.⁵⁹ Because most biologic products are delivered to patients in clinics, hospitals, and doctor's offices, or other medically-supervised settings, shifting to another biologic product is typically more costly because it requires restocking inventory and retraining nurses and healthcare providers.⁶⁰

4. Fewer Payor Strategies to Incentivize Rapid Uptake of FOBs

Biologic drug products are typically delivered to patients by healthcare providers as part of medical treatments (e.g., dialysis treatments or oncology treatments) and reimbursed by health insurers as part of patients' medical benefits rather than the pharmacy benefits. This situation contrasts with small-molecule drug products which are dispensed by pharmacists to the patients and reimbursed by the insurance providers as

FDA Considerations: Discussion by National Regulatory Authorities with World Health Organization (WHO) On Possible International Non-proprietary Name (INN) Policies for Biosimilars (Sept 1, 2006) ("The world community may ultimately decide that INN policy for this class of products should be treated differently than that for small-molecule drugs."), *available at* <http://www.fda.gov/cder/news/biosimilars.htm>.

⁵⁶ CVS Caremark Comment (12/22/08) at 4 ("Given the uncertainty surrounding the equivalence of innovator and follow-on biologics, PBM, payors and physicians are more likely to be focused on clinical information and dialogue about the prudence of switching to a particular follow-on biologic or innovator drug. This ad hoc, non-uniform approach will ultimately drive the adoption of follow-on biologics, but at a pace than seen with generic small-molecule drugs.").

⁵⁷ *Id.*

⁵⁸ CBO S. 1695 Report; Ahlstrom at 43.

⁵⁹ Golding at 64-65; CVS Caremark Comment (12/22/08) at 1. Specialty pharmaceuticals often are distributed in separate channels to preserve the viability and safe administration of the products.

⁶⁰ Golding at 64-65.

part of the patients' pharmacy benefit.⁶¹

Traditional payor strategies used to manage pharmacy benefits that incentivize rapid shifting of patients from branded drugs to lower-priced generic drugs – for example, by requiring higher co-pays from patients for drugs off the formulary – are likely to be of limited use for biologic drugs. Consequently, payors will have fewer strategies to incentivize the rapid uptake of lower-priced FOBs, especially biosimilars.⁶² In addition, the reimbursement methodologies used by Centers for Medicare and Medicaid Services (“CMS”) for biologic drugs are likely to be important factors affecting the market impact of FOBs and pricing of FOBs.⁶³

Because of these four characteristics, payors, branded manufacturers, and FOB manufacturers forecasted that pioneer manufacturers are likely to maintain market share for several years even after FOB entry. They predicted that market share acquisition by FOBs would be modest, lagging substantially behind the sometimes blistering competitive pace established by generic small-molecule entrants.⁶⁴ Several commenters

⁶¹ For example, costs for senior citizens for biologic drugs are generally reimbursed under Medicare Part B, rather than Part D. See CBO BUDGET OPTIONS at 106, 126-27; AARP Comment (12/22/08) at 1; CVS Caremark Comment (12/22/08) at 7.

⁶² Alhstrom at 43-45 (noting that insurance plans and PBMs immediately cover generic drugs and immediately implement tools to switch their patients from the brand to the generic small-molecule drug which results in the 80-90% share shift to generics a market dynamic that she does not predict will be duplicated in the biologic-FOB market experience any time in the near future.”); Buckley at 47 (“It’s going to be the decision of the physician and the patient as to whether or not a drug will be substituted for a therapy that they may already be on or a therapy that they may be considering taking.”); see also Golding at 49.

⁶³ Mylan Comment (1/5/09) at 5-6. In contrast to the authority CMS has to incentivize the use of generic small-molecule products, currently, there is no express statutory authority for the CMS to reimburse FOBs in such a way as to incentivize utilization of the lowest priced biologic product. CVS Caremark Comment (12/22/08) at 7; Miller at 213-14. The Congressional Budget Office has indicated that a change to the Medicare Part B reimbursement methodologies would be needed to maximize savings from FOB products. See generally CBO BUDGET OPTIONS; CVS Caremark Comment (12/22/08) at 7; Heldman at 29-31 (“The current formula under Medicare provides a financial incentive for physicians and hospitals, when using the drugs in an outpatient setting to use the higher cost drugs...because Medicare reimburses at the average sales plus a 6 percent markup. In addition, current law requires Medicare [to give] a follow-on biologic that the FDA doesn’t deem interchangeable . . . a separate billing code....”); Amgen, Inc. v. F. Hoffmann-La Roche Ltd., 2008 U.S. Dist. LEXIS 77343 at *169-73 (D. Mass. Oct. 2, 2008) (noting that the court could not conclude that entry by Roche’s branded EPO biologic drug, Mircera, would reduce Medicare Part B reimbursement for EPO drugs).

⁶⁴ CVS Caremark Comment (12/22/08) at 4; Buckley at 52-53; Bernstein Research Comment (9/29/08) at 1-2; BIO Comment (9/30/08) at fn. 2.; Amgen Comment (9/30/08) at 5 (“The combination of these factors will make it very unlikely that biosimilar products will bring about the price differential that generic products do.”); Momenta Comment (9/30/08) at 3 (“The likely competitive effect of a follow-on biologic entering the market is the gradual reduction in prices of the biologic.”); Hospira Comment (9/30/08) at 1 (“The best estimate is that the biosimilar EPOs [in the EU] appear to be priced approx 25 - 30 percent below the innovator’s price prior to the entry of any biosimilar.”); CCPM Comment (9/30/08) at 2 (“According to the March, 2008, edition of the Red Book, Omnitrope’s price is a 34% discount from the original product.”); Grabowski, *White Paper* at 6 (“The extent of entry will likely be much lower for FOBs

concluded that uptake of FOBs will likely be “slower and less extensive than for many small-molecule drugs.”⁶⁵ They estimated that the uptake for FOBs will range between 10 percent and 30 percent.⁶⁶ They also noted that the market share uptake of FOBs will be correlated to the price which in turn is affected by the sums needed to generate clinical trial data required by the FDA to obtain approval.⁶⁷

Panelists noted that as the market gained positive experience with FOBs, market uptake of FOBs could increase.⁶⁸ Conversely, they also predicted that if the market had negative experiences with FOBs from safety or efficacy issues (immunogenicity, heparin like contamination or problems akin to the generic drug scandals of the 1980’s), then FOB uptake could also be significantly dampened.⁶⁹

C. Market Experience with Biosimilar Entry

Market experience with both pioneer and FOB competitors confirms that FOB competition is likely to resemble branded competition rather than generic competition as seen for small-molecule drug products. The European Union adopted an approval process for follow-on biologics in 2004.⁷⁰ To date, the European Medicines Agency has approved biosimilars for three products: (1) EPO (erythropoietin stimulating agent or “ESA”) to treat anemia; (2) human growth hormone (“HGH”) to treat children with small stature, and other conditions associated with deficiencies of the naturally occurring hormone; and (3) G-CSF (Granulocyte-Colony Stimulating Factor) to stimulate production of white blood cells needed to fight infection. In the U.S., the FDA has

than for conventional generic drugs, reflecting differences in market size and high fixed costs of entry for many biologics. Average price effects and rates of FOB uptake for innovator products are likely to be limited in the short run due to the low number and timing of entry of FOBs, limitations to perceived substitutability between innovator biologics and FOBs on the part of physicians and patients, incentives for limited price-based competition between FOBs and innovator products....”); Grabowski, *Entry and Competition*, at 449.

⁶⁵ See Grabowski, *White Paper* at 2.

⁶⁶ *Id.*; Heldman at 25, 27.

⁶⁷ Heldman at 25, 27; Brugger at 39; Urlep at 56 (“We have to invest into primary marketing to overcome this with our data, which we created during the development programs.”); Hospira (Wilkie Farr) Comment (12/22/08) at 2 (“Without an ‘interchangeable’ designation, biosimilar companies would be compelled to invest significant sums to market and promote biosimilars, thus driving up the cost to the consumer.”).

⁶⁸ Grabowski at 42.

⁶⁹ Brugger at 74.

⁷⁰ Linda Horton, *The European Experience with Follow-on Biologics Legislation at FTC Roundtable: Emerging Healthcare Competition and Consumer Issues* (Nov. 21, 2008) at 3 [hereinafter “Horton Presentation”].

approved two biosimilar HGH products pursuant to the FD&C Act.⁷¹ The following two sections describe the market competition for EPO and HGH.⁷²

1. EPO Market Experience in the European Union

Panelists and commenters explained that seven EPO biologic manufacturers market their products in Germany, three of which are biosimilars (products 5-7):

- (1) Amgen's Aranesp,
- (2) Johnson & Johnson's Eprex/Erypo,
- (3) Roche's NeoRecormon,
- (4) Roche's Mircera,
- (5) Hospira's Retacrit,
- (6) Novartis' Binocrit, and
- (7) Shire's Dynepo.⁷³

As of November 2008, the multiple biosimilar entrants had attained a combined market share in Germany of between 14 to 30 percent with price discounts estimated at about 25 percent off the branded price several years after entry.⁷⁴ The reported results of international sales from the first quarter of 2009 appear to confirm that pioneer firms retain a significant first mover advantage. For example, Amgen states that Aranesp's

⁷¹ See Appendix B for a discussion of the statutory authority that permits the FDA to approve a limited number of biosimilar products under the FD&C Act.

⁷² Although the E.U. approved biosimilar filgrastim on February 13, 2009, market experience was too limited to include in this report. See Press Release, Sandoz, Sandoz Receives European Commission Approval for Biosimilar Filgrastim (Feb. 13, 2009), available at http://www.sandoz.com/site/en/media_room/press_releases_news/090213.shtml; Hospira Comment (May 11 2009) at 3, Amgen, Q1 2009 Earnings Call, at 19-20 (April 23, 2009). In Europe, the pioneer G-CSF products consist of Amgen's Neupogen (filgrastim), Amgen's Neulasta (pegylated filgrastim) and Chugai's Granocyte (lenograstim), while the biosimilar products consist of Teva's Tevagrastim, Ratiopharm Ratiograstim and Ratiopharm filgrastim, CT Arzneimittel's Biograstim, Novartis' Zarzio (marketed by Novartis' Sandoz division), and Filgrastim Hexal (marketed by Novartis' Hexal division).

⁷³ Hospira, Inc. ("Hospira") and STADA Arzneimittel AG co-market their product Retacrit/Silapo in Germany. Market shares for Novartis' Binocrit, Novartis' Epoetin alpha Hexal and Medice' Arzneimittel Putter GmbH & Co KG's Abseamed are represented together. On February 17, 2009, Shire plc. ("Shire") discontinued selling Dynepo in Europe for commercial reasons, and its marketing authorization was rescinded in March, 2009. See <http://www.emea.europa.eu/humandocs/PDFs/EPAR/dynepo/12666909en.pdf>.

⁷⁴ Bernstein Research Comment (9/29/08); Paul Heldman, *Follow-On Biologic Market: Initial Lessons and Challenges Ahead at FTC Roundtable: Emerging Healthcare Competition and Consumer Issues* (Nov. 21, 2008) at 7 [hereinafter "Heldman Presentation"]; Heldman at 26-27; Lane at 36 ("on a unit basis [we] have actually captured 23 percent of the first gen market"); Novartis Comment (9/29/08) at 2-3. Some of the share estimates differ because some estimates are calculated based on units while others are based on different measures of sales. *Id.* See also Amgen, Q1 2009 Earnings Call, at 19-20 (April 23, 2009).

market share in dialysis patients has increased slightly even two years after biosimilar and other branded competitors have entered the market.⁷⁵

2. HGH Market Experience in the European Union and the United States

Panelists and commenters also discussed the limited price competition and market share shift to biosimilars in the HGH markets in the E.U. and U.S. In April 2006, Novartis launched its biosimilar HGH product, Omnitrope, which referenced Pfizer's Genotropin, in Germany and Austria. In December 2006, BioPartner launched the second HGH product, Valtropin, in the E.U., which referenced Eli Lilly's Humatrope.

By leveraging its global R&D, Novartis launched Omnitrope in the United States in 2007.⁷⁶ The second HGH biosimilar entrant in the United States was Teva with Tev-Tropin.⁷⁷ There are five other branded HGH products in the U.S. market:

- Pfizer's Genotropin
- Eli Lilly's Humatrope
- Novo Nordisk's Norditropin
- Serono's Saizen
- Genentech's Nutropin (Genentech, majority-owned by Roche)⁷⁸

As of November 2008, combined U.S. market shares of the two biosimilars amounted to about four percent.⁷⁹ Panelists' best estimates of the price discounts in the U.S. for HGH biosimilar drug products ranged from 10 to 40 percent off the branded HGH products' prices depending upon the purchaser, while branded HGH prices had increased.⁸⁰ As

⁷⁵ See Amgen, Q1 2009 Earnings Call, at 19-20 (April 23, 2009) (stating that Hospira's Retacrit and the other biosimilars together account for only 5 percent market share).

⁷⁶ For a discussion of the novel issues involved with the approval of Omnitrope, see *Sandoz, Inc. v. Leavitt*, 427 F. Supp. 2d 29 (D.D.C. 2006); see generally FDA's Second Response to Omnitrope CPs; Letter from Janet Woodcock, Director, CDER, FDA to Petitioners (October 14, 2003), available at <http://www.fda.gov/ohrms/DOCKETS/dailys/03/oct03/102403/03p-0408-pdn0001.pdf> [hereinafter "FDA's First Response to Omnitrope CPs"]. When the FDA approved Sandoz's Omnitrope on May 31, 2006, it did not rate Omnitrope as therapeutically equivalent, to and automatically substitutable for Genotropin. See Letter from Paulo Costa, President & CEO, Novartis Corp. to Frank Pallone, Jr., Chmn. and Nathan Deal, H. Subcomm. on Health (May 1, 2008) at 9-10, available at http://energycommerce.house.gov/Press_110/110-ltr.050108.respto040308.Novartis.pdf.

⁷⁷ Heldman at 23; Citigroup 2006 FOB Guidebook at 2; Bernstein Research Comment (9/29/08) at 12-13.

⁷⁸ *Id.*; FDA's Second Response to Omnitrope CPs at 7.

⁷⁹ Heldman at 28, Heldman Presentation at 3-6.

⁸⁰ See Heldman at 28, Heldman Presentation at 3-6; CBO S.1695 Report. Heldman notes that aggressive discounts offered in the market to PBMs and other payors are generally non-public and not captured in the WAC data available from IMS and other sources. Branded firms compete on prices not by lowering the list, WAC or AWP to all customers, but by offering discounts off those prices to the most price sensitive,

discussed above, pioneer manufacturers offer discounts to their most price sensitive, sophisticated, and largest purchasers; these discounts are negotiated individually and typically are not publicly available.⁸¹ Both Novartis and Teva supported their biosimilar products with marketing and sales efforts.⁸²

D. Likely Pricing Effect of Interchangeable FOBs

Panelists and commenters expressed a range of price discount predictions if and when technology allows interchangeable FOBs to enter the market. For ease of discussion, some panelists and commenters referred to interchangeable FOBs as “biogeneric” drugs. Panelists predicted that if biogeneric applicants could, for example, rely on analytical data rather than clinical trials to show equivalent efficacy, and not be required to engage additional comparability and immunogenicity trials, then biogenerics will generate greater consumer savings than biosimilars.⁸³ And conversely, if a biogeneric pathway were more costly and rigorous than the process for new drug approvals, panelists predicted no biogeneric FOB entrants would use such a pathway as “manufacturers would be better off pursuing a full approval.”⁸⁴

One commenter explained that savings in marketing and selling expenses should translate into lower sales price for a biogeneric product than a biosimilar product.⁸⁵ An FOB manufacturer explained that only interchangeable biogeneric, not biosimilar, products offer the greatest price competition.⁸⁶ This increased price competition,

sophisticated, and largest purchasers. See Heldman at 24-25; FTC PBM REPORT at 48-54; LEVY REPORT at 183; see generally CBO, *Research and Development in the Pharmaceutical Industry* at 48; CBO, *Increased Competition from Generic Drugs*, at 27-30.

⁸¹ See FTC PBM REPORT at 48-54.

⁸² See Urlep at 34; Lane at 36.

⁸³ See Brugger at 74 (“[W]hat is very important to us to make continued investment in this field is a very clear path towards interchangeability, and what that does is allows companies like ours to innovate in the analytical space and not in the clinical trial space. These clinical trials are a very crude way to detect similarities or differences between these very complex molecules, and the way that we will truly understand these complex macro molecules in the future is by innovating in this analytical space.”); Behrman at 77 (“I couldn’t agree ... more that the real advances will come in the analytics and the ability to, to the best of our ability, realize how similar or different these products are and may minimize or shorten or decrease the extent to which certain types of clinical trials are necessary.”).

⁸⁴ Hospira (Wilkie Farr) Comment (12/22/08) at 3 (“If a company pursuing the development of a biosimilar/biogeneric cannot reference any of the innovator’s preclinical or clinical data, there would be no incentive to embark on an abbreviated approval pathway.”).

⁸⁵ Hospira Comment (9/30/08) at 1; *but see* BIO Comment (9/30/08) at 3-4 (presumed biogenerics are more expensive to get approved and priced higher than biosimilars).

⁸⁶ GPhA Comment (9/30/08) at 1-2; *see also* Novartis Comment (9/29/08) at 3 (explaining that interchangeability would “enable direct, head-to-head competition to occur based on price factoring in the front-loaded investment in the research and development of an FOB without the additional cost of a ‘back-loaded’ investment in the advertising, promotion, and detailing of an FOB. Consequently, competing

however, is likely to be greater than price competition among biosimilars, but not as great as generic drug price competition seen with small-molecule generic drugs.⁸⁷

However, at least one panelist disagreed stating, “[i]nterchangeability will not necessarily provide greater economic benefit from biosimilar market entry.” He asserted that this prediction is erroneous because it is based on the false assumption that biogeneric products would be “interchangeable” and approved without more clinical testing than biosimilars.⁸⁸ One commenter stated that not only was biogeneric entry not possible, but the effects on cost savings provided by biogenerics were too speculative to predict at this point.⁸⁹

E. Conclusions About the Likely Market Impact of FOB Entry

An abbreviated approval process for follow-on biologic drugs is likely to be an efficient way to bring a biosimilar drug product to market. The FOB applicant can save time and money by not engaging in the full pre-clinical and clinical tests and, as a result, it can enter the market at a price lower than the pioneer drug product.

Competition from FOB drug entry is likely to resemble brand-to-brand competition rather than brand-to-generic drug competition for small-molecule products. Two or three FOB manufacturers are expected to seek entry in large markets due to the significant time and expense expected to develop an FOB drug product. They are likely to introduce their drug products at price discounts between 10 and 30 percent of the pioneer products’ price to the most price-sensitive customers. Pioneer manufacturers are expected to respond aggressively and offer competitive discounts. This price competition is likely to lead to an expanded market and greater consumer access.

The lack of automatic substitution will slow significant market share acquisition by FOB products. The difficult and costly administration, training, payment, and reimbursement of specialty drugs makes it likely that there will be few entrants, despite the multi-billion dollar size market opportunities offered by many biologic products losing their patent protection in the next 10 years. Moreover, traditional payor incentives used in the retail pharmacy setting, such as co-pay differential and formulary tiering to incentivize utilization of low-priced drugs, are unlikely to be used in the specialized drug setting in which many biologics are dispensed, such as hospitals and outpatient clinics,

FOBs that are designated as interchangeable can be anticipated to achieve more rapid and ultimately more substantial market share penetration than those that are not.”).

⁸⁷ See Amgen Comment (9/30/08) at 6; CBO S. 1695 Report; Momenta Comment (9/30/08) at 4 (“A designation of “interchangeability” by FDA would significantly increase the competitive impact of a follow-on biologic product and consequently the potential for cost savings.”); Novartis Comment (9/29/08) at 9, 11, 24.

⁸⁸ BIO Comment (12/22/08) at 1; Heldman at 24-28.

⁸⁹ BIO Comment (12/22/08) at 3; PhRMA Comment (9/30/08) at 1.

and other clinical settings. As a result, pioneer manufacturers are likely to retain 70 to 90 percent of their market share after FOB entry.

The likely effect of FOB entry contrasts markedly from small-molecule generic drug competition. Soon after small-molecule generic drug entry occurs, the branded product loses most of its market share. This loss of market share occurs because of state substitution laws and payor incentives that permit pharmacies to substitute a prescription for a branded product to a generic product without physician consent. When a market includes eight or more generic products, prices can be discounted up to 80 percent of the branded price.

The Commission is mindful that the likely competitive effects of FOB entry described in this chapter are based on agreement among pioneer manufacturers, potential FOB applicants, and payors as to future conditions. The likely competitive effects of FOB competition could change if technology breakthroughs occur, biosimilar safety issues arise, health insurance coverage expands, or payor and reimbursement strategies change, among others. In sophisticated industries such as biotechnology, external conditions can and do change and often alter expectations of profit-maximizing firms.⁹⁰ This industry, however, has shown significant ability to adapt and thrive under new market conditions.⁹¹ The Commission expects the robust and dynamic market conditions of the biologic drug industry to continue with the entry of FOB drug products.

⁹⁰ See Charles E. Phelps, *Managing the Market: Regulation and Technical Change in Health Care*, HEALTH ECONOMICS, at 498-546 (3d ed. 2003).

⁹¹ See Iain M. Cockburn, *The Changing Structure of the Pharmaceutical Industry*, 23 HEALTH AFFAIRS 1:10-22, 14 (2004).

CHAPTER 2 PATENT PROTECTION AND MARKET INCENTIVES ARE LIKELY TO CONTINUE TO PROVIDE ROBUST INNOVATION INCENTIVES AFTER ENTRY OF FOLLOW-ON BIOLOGIC DRUGS

I. INTRODUCTION

The introduction of FOB competition raises the question of whether, in addition to patent protection and market-based pricing, pioneer biologic drug products need an exclusivity period, a “branded exclusivity period,” that restricts FOB competition by prohibiting the FDA from approving an FOB product for some period of time to promote innovation in biologic drug markets.⁹² Pioneer biologic drug manufacturers have suggested that a 12- to 14-year branded exclusivity period is necessary to incentivize innovation.⁹³ The length of this branded exclusivity period is based on a model that estimates the time it takes a pioneer manufacturer to recoup its investment to develop and commercialize a typical biologic drug (the “Nature model”).⁹⁴

This chapter explains that the main argument for a branded exclusivity period of 12 to 14 years is to compensate for the perceived failures of the patent system to reward, protect, and incentivize biologic drug innovation.⁹⁵ To understand whether such a branded exclusivity period is necessary, and the likely effects of such a period, this chapter summarizes the comments and relevant economic literature on how biologic drugs are developed and the role of the patent system in driving these innovations.

⁹² Other ways to incentivize innovation include tax credits for R&D costs similar to the tax credits used for orphan drugs. See Orphan Drug Act, 21 U.S.C.A. § 360aa-dd (2009). Alternatively, one commenter suggested that a new regulatory scheme be developed to allow for the reporting of R&D costs by pioneer manufacturers and then to have FOB entrants repay a share of these costs. See Essential Action Comment (12/22/08) at 4. This system may be difficult to establish and administer because FOBs are similar, not identical to the branded product, and may rely on different FDA findings of safety and effectiveness of the branded product to support regulatory approval.

⁹³ This report uses the term “branded exclusivity” rather than “data exclusivity” because current legislative proposals permit an FOB applicant to rely on FDA’s finding or conclusion that an approved pioneer drug is safe and effective. This reliance does not involve disclosure to the FOB applicant, or to the public, of the data in the pioneer manufacturers’ application. See FDA to Petitioners (May 30, 2006) at 6, available at <http://www.fda.gov/ohrms/dockets/dockets/04P0231/04P-0231-pdn0001.pdf>. Further, reliance on the FDA’s findings of safety and efficacy of the pioneer biologic provides much less of a benefit in the biologic context than in the small-molecule context, because the FOB will still have substantial R&D expenditures, including clinical testing. See *infra* Ch. 1 at 9, 14-15.

⁹⁴ Henry Grabowski, *Follow-on Biologics: Data Exclusivity and the Balance Between Innovation and Competition*, 7 NATURE REVIEWS DRUG DISCOVERY 479, 483 (June 2008).

⁹⁵ American Enterprise Institute (“AEI”) Comment (12/10/08) at 5 (“[D]ata exclusivity is a tool that comes into play when patents fail to provide reasonable protection for innovation.”); Henry Grabowski *et al.*, *Updating Prior Analyses and Responding to Critiques*, Duke Univ. Dept. Econ. Working Paper, No. 2008-10 (Dec. 22, 2008) at 3 (“[E]xclusivity periods are essential to compensate for some important shortcomings in patent protection for biologics.”); Duke University Comment (12/23/08) at 1 (“Data exclusivity periods . . . are an “insurance policy.”).

The patent system is the primary means by which the government grants exclusive rights to promote innovation. Patent protection and market-based pricing enables biotechnology firms to increase their expected profits from investments in R&D, thus fostering innovation that would not occur without patents' exclusionary rights.⁹⁶ Congress and the courts set patent policy with a conscious eye towards maintaining an appropriate balance with competition policy, which also promotes innovation, as the best means to benefit consumers.⁹⁷

Nothing about the introduction of FOB drug products changes the relationship of pioneer biologic drug products to the patents protecting them. As a result, patent protection should continue to incentivize biotechnology innovation, even after enactment of an approval process for FOB drugs. Pioneer biologic drugs are covered by more and varied patents than small-molecule branded products, including manufacturing and technology platform patents. Moreover, there is no evidence that patents claiming a biologic drug product have been designed around more frequently than those claiming small-molecule products.

Even if the FOB manufacturer were to design around the patents claiming a pioneer biologic drug product and enter prior to patent expiration, the effect of FOB entry is unlikely to cause the precipitous decline in the pioneer product's revenues that generic drug entry causes. FOB drugs are likely to garner only 10 to 30 percent market share of an expanded market, rather than nearly 100 percent of the market share from a branded small-molecule drug manufacturer. The pioneer biologic drug manufacturer can continue to earn significant revenues years after FOB entry.

The use of patents to incentivize innovation is especially strong if the FOB approval process does not contain special features similar to the ones in Hatch-Waxman that incentivize an early start to patent challenges that is prior to FDA approval of the generic drug. (These issues are discussed in Chapters 3 and 4.) These early patent challenges are unique to the generic drug industry and, if applied in the FOB drug context, undermine the ability of the patent to incentivize innovation.

Market experience shows that pharmaceutical products already compete against other branded entrants and that this competition benefits consumers by increasing the pace and scope of innovation as well as price competition. Currently, pioneer or first-in-class branded products engage in a race with other branded competitors to bring products

⁹⁶ F.M. Scherer & David Ross, *INDUSTRIAL MARKET STRUCTURE AND ECONOMIC PERFORMANCE*, 3d Ed. 621 (1990).

⁹⁷ The Supreme Court has emphasized the "careful balance" embodied in the patent system: "From their inception, the federal patent laws have embodied a careful balance between the need to promote innovation and the recognition that imitation and refinement through imitation are both necessary to invention itself and the very lifeblood of a competitive economy." *Bonito Boats, Inc. v. Thunder Craft Boats, Inc.*, 489 U.S. 141, 146 (1989).

to market.⁹⁸ Over the last three decades, the head start of the first-in-class drug product has decreased as the average lead time of the first-in-class product shrank from 8.2 years during the 1970s to 2.25 years in the 1990s. This limited head start for the first-in-class drug product has not dampened R&D incentives and may, in fact, be optimal for rewarding past innovation while allowing competition to incentivize future innovation.⁹⁹ Because FOB entry is likely to have a competitive effect similar to that caused by entry of another branded competitor, it is likely that FOB entry will have a similar effect on innovation.

Congress has implemented exclusivity periods to encourage the development of new and innovative drug products when the drug molecule is in the public domain, and therefore not patentable. The Hatch-Waxman Act provides a five-year exclusivity period to incentivize the development of new chemical entities and it provides a three-year exclusivity period for new clinical investigations (“NCT”) of small-molecule drugs. In other instances, Congress has implemented an exclusivity period when market-based pricing has not provided sufficient incentive to test drug products for children or small patient populations.

Central to each of these exclusivities is a public policy trade-off: a restriction on competition is provided in return for a development of a new drug product or new use of an existing product. A 12- to 14-year exclusivity period for pioneer drugs, however, departs sharply from this basic trade-off, because it does not spur the creation of a new product or indication. The product has already been incentivized through patent protection and market-based pricing.

The potential harm posed by such a period is that firms will direct scarce R&D dollars toward developing low-risk clinical and safety data for drug products with proven methods of action rather than toward new inventions to address unmet medical needs. Thus, a new 12- to 14-year exclusivity period imperils the efficiency benefits of an FOB approval process in the first place and it risks over-investment in well-tilled areas.

This chapter then summarizes a critique of the Nature model. The model as currently structured contains numerous methodological and conceptual weaknesses that render its results too imprecise and non-robust to inform discussions about the ideal length of any branded exclusivity period. A model that balances the benefits of FOB competition with the costs of potentially forsaking marginal branded drug development projects would be more informative than the Nature model’s approach.

⁹⁸ See Joseph DiMasi & Cherie Paquette, *The Economics of Follow-on Drug Research and Development*, 22 PHARMACOECONOMICS Supp 2:1-14, 10 (2004). Although this study examined pharmaceutical products primarily, it included several biologic drugs as well.

⁹⁹ F.M. Scherer, *Markets and Uncertainty in Pharmaceutical Development* 13 (FACULTY RESEARCH WORKING PAPERS SER., HARV. U. JOHN F. KENNEDY SCHOOL OF GOV’T, 2007), available at [http://ksnotes1.harvard.edu/Research/wpaper.nsf/rwp/RWP07-039/\\$File/rwp_07_039_scherer.pdf](http://ksnotes1.harvard.edu/Research/wpaper.nsf/rwp/RWP07-039/$File/rwp_07_039_scherer.pdf).

II. THE IMPORTANCE OF PATENT PROTECTION TO THE NEW DRUG RESEARCH AND DEVELOPMENT PROCESS

A. New Drug Research and Development Process

Pharmaceutical innovation for new drug products is lengthy, expensive, highly risky, and involves a multitude of public- and private-sector entities.¹⁰⁰ Pharmaceutical innovation begins with basic scientific research. Much of the funding of basic medical research comes from the National Institutes of Health or other government sources, angel investors and corporations, not venture capitalists.¹⁰¹ This funding covers basic research up until proof of concept, which is usually demonstrated by preclinical findings.¹⁰² This basic medical understanding of disease pathways and processes has led to the commercialization of two categories of biologic drugs: (1) recombinant proteins; and (2) monoclonal antibodies.¹⁰³

Once proof of concept has been attained, private investment from angel investors, corporate, and venture capital funding continues the development of these inventions

¹⁰⁰ See F.M. Scherer, *Pharmaceutical Innovation*, (John F. Kennedy School of Government, Harvard Univ., Working Paper No. RWP07-004, 2007) available at <http://ksgnotes1.harvard.edu/Research/wpaper.nsf/rwp/RWP07-004>; Scherer, *Markets and Uncertainty*, at 11; see also U.S. Cong., Office of Technology Assessment (“OTA”), *Pharmaceutical R&D: Costs, Risks and Rewards*, at 6 (1993), available at <http://www.princeton.edu/~ota> (follow “OTA publications” hyperlink and use search engine there to find article by title) [hereinafter “Pharmaceutical R&D”].

¹⁰¹ Public policy to increase the U.S. expenditures for research, development and commercialization of federally-funded inventions led to enactment of The University and Small Business Patent Procedures Act of 1980 (also known as “The Bayh-Dole Act”), 35 U.S.C.A. § 200 *et seq.* (2009). This act provides universities and small businesses the right to patent federally funded inventions. Corporations and larger businesses were afforded these same rights pursuant to the Trademark Clarification Act of 1984. 15 U.S.C.A. § 1501 (2009); 35 U.S.C.A. § 210(c) (2009). Privatization of government-funded research was deemed necessary because of a market failure to allocate risk capital to early-stage inventions. Since passage of the Bayh-Dole Act, university-based research has increased by over 800%. See Lewis M. Branscomb and Philip Auerwald, *Between Invention and Innovation: An Analysis of Funding for Early Stage Technology Development*, prepared for Nat’l Inst. of Standards and Technology (“NIST”), Dept. of Commerce (2002), available at <http://www.atp.nist.gov/eao/gcr02-841/contents.htm>. While government funds are used on a variety of novel scientific research, corporate funding typically is incremental innovation to support its pre-existing core business, and to “advance its established product and process technologies to better serve existing markets.” *Id.* at 4.

¹⁰² Jerry G. Thursby & Marie Thursby, *Enhanced: University Licensing and the Bayh-Dole Act*, SCIENCE, Aug. 22, 2003, at 1052, available at <http://www.sciencemag.org/cgi/content/full/301/5636/1052>.

¹⁰³ Steven Kozlowski, *Protein Therapeutics and the Regulation of Quality: A Brief History*, BIOPHARM INTERNATIONAL (Oct. 1, 2007), available at <http://biopharminternational.findpharma.com/biopharm/article/articleDetail.jsp?id=462759&sk=&date=&pageID=2>. In addition to these two classes of therapeutic drug treatments, three additional classes of biotechnological products include: (1) vaccines, which typically are preventative treatments but are under investigation for use as therapeutic treatments; (2) cell therapies and (3) gene therapies which are in clinical development.

through clinical development of a drug candidate.¹⁰⁴ After late stage clinical development, private corporations typically begin to scale-up manufacturing and marketing efforts.¹⁰⁵ The R&D process for developing biologic drugs lasts, on average, 10 to 12 years.¹⁰⁶

Pioneer biologic manufacturers also engage in a race to screen, patent, and develop their products.¹⁰⁷ These races are often propelled by a new medical threat or scientific advances that suggest a new line of therapy.¹⁰⁸

A study of first-in-class drugs approved by the FDA from the 1960s through the 1990s shows that increasingly, multiple firms target the same disease, therapy or biologic pathway, and as a result, nearly every therapeutic class has had multiple branded competitors. Branded competitors' R&D occurs in parallel. For example, in the 1990s, for all drug classes in which a first-in-class drug was approved, clinical testing for at least one branded competitor's drug occurred before FDA approval of the first-in-class drug.¹⁰⁹ The head start of the first-in-class drug product has decreased over the last three decades, shrinking markedly from 8.2 years during the 1970s to 2.25 years in the 1990s.¹¹⁰

Competition does not stop once FDA approval is obtained. Biologic drug manufacturers in particular seek to expand the market opportunity for their products by obtaining additional indications for diseases that share biologic pathways; for example, HGH indications for Turner's syndrome and pituitary dwarfism, Tumor Necrosis Factor ("TNF") inhibitors for both Crohn's Disease and rheumatoid arthritis, and Vasoendothelial Growth Factor ("VEGF") inhibitor for lung cancer and colorectal

¹⁰⁴ See NIST, DEP'T. OF COMMERCE, BEYOND MEASURE: A PROFILE OF ATP HEALTH CARE INVESTMENTS (2003), available at <http://www.atp.nist.gov/atp/brochures/healthcare.pdf> (estimating that federal funding accounts for 21 to 25 percent of funding during the "valley of death" period between basic research and product development).

¹⁰⁵ See Branscomb, *Between Invention and Innovation*, at Figure 2, p. 33, see also Tanuja V. Garde, *Supporting Innovation in Targeted Treatments: Licenses of Right to NIH-funded Research Tools*, 11 MICH. TELECOMM. TECH. L. REV. 249, 277 (2005), available at <http://www.mtlr.org/voleleven/garde.pdf>.

¹⁰⁶ See Joseph DiMasi et al., *The Price of Innovation: New Estimates of Drug Development Costs*, 22 J. Health Econ. 151, 162, 166 (2003) (estimating that average time from synthesis of a compound to initial human testing is 52.0 months, from the start of clinical testing to marketing approval is 90.3 months, and the total time is approximately 142 months [11 years, 10 months] for small-molecule drugs); see also Grabowski, NATURE, at 481.

¹⁰⁷ DiMasi, *The Economics of Follow-on Drug Research and Development*, at 10.

¹⁰⁸ Scherer, *Markets and Uncertainty*, at 13.

¹⁰⁹ DiMasi, *The Economics of Follow-on Drug Research and Development*, at 9.

¹¹⁰ *Id.*; Scherer, *Markets and Uncertainty*, at 13.

cancer. These incremental innovations lead to “improvements that over time can yield substantial benefits.”¹¹¹

B. The Importance of Patent Protection Incentives for Innovation

Patent protection fuels this R&D engine.¹¹² To obtain a patent, an invention (*i.e.*, a product, a process, machine, or composition of matter) must be novel, non-obvious, and useful. A patentee also must disclose clearly the invention. Economic literature has described how this property right enables biotechnology firms to increase their expected profits from investments in R&D, thus fostering innovation that would not occur but for the prospect of a patent.¹¹³

The FTC, in its 2003 Report, “To Promote Innovation: The Proper Balance of Competition and Patent Law and Policy,” described how innovation in the biotechnology and pharmaceutical industries is highly dependent on patent protection, more so than any other industry.¹¹⁴ Stand-alone innovation in these two industries is costly and unpredictable, requiring significant amounts of pioneering research to discover and test new drug products. By preventing rival firms from free riding on discoveries, patents allow pioneer firms to recoup the substantial capital investments made to discover, test, and obtain regulatory approval of new drug products. Patents also are necessary to attract the capital to fund high-risk investment in the biotechnology industry.¹¹⁵

The FTC Patent Report explained how pharmaceutical and biotech firms use the patent information disclosures required by the patent statutes to direct their R&D into

¹¹¹ See *e.g.*, AEI Comment (12/10/08) at 2 (post approval development of novel biologics continues as science evolves); see also John Calfee, *The Golden Age of Medical Innovation*, THE AMERICAN (March/April 2007), available at <http://www.american.com/archive/2007/march-april-magazine-contents/the-golden-age-of-medical-innovation>.

¹¹² See, *e.g.*, *Patent Reform: The Future of American Innovation*, Hearing Before the S. Comm. on the Judiciary, 110th Cong. (2007) (statement of Kathryn L. Biberstein, Senior Vice President, Alkermes, on behalf of the Biotechnology Industry Organization), available at <http://judiciary.senate.gov/hearings/hearing.cfm?id=2803>.

¹¹³ F.M. Scherer & David Ross, INDUSTRIAL MARKET STRUCTURE AND ECONOMIC PERFORMANCE, 621 (3d ed. 1990); see also *Amgen, Inc. v. F. Hoffmann-La Roche Ltd.*, 2008 U.S. Dist. LEXIS 77343 at *169-73 (D. Mass. Oct. 2, 2008 (“Of course, the public derives significant benefits from the innovation generated by the economic incentives in our patent system.”)).

¹¹⁴ See FEDERAL TRADE COMM’N, TO PROMOTE INNOVATION: THE PROPER BALANCE OF COMPETITION AND PATENT LAW AND POLICY (2003), Ch. 3 at 1 [hereinafter “FTC PATENT REPORT”].

¹¹⁵ *Id.*, see also Arti K. Rai, *Knowledge Commons: The Cost of the Biopharmaceutical Industry*, FIRST MONDAY (June 2007) (“Small biotechnology firms rely on patents, often on technology that is far removed from an end product, for purposes of deterring misappropriation when they market their technology. Patents also help small biotechnology firms negotiate vertical R&D alliances with pharmaceutical firms. For their part, pharmaceutical firms rely on patents on end product drugs for purposes of recouping research and development costs. [footnotes omitted.]”), available at <http://firstmonday.org/htbin/cgiwrap/bin/ojs/index.php/fm/article/view/1909/1791>.

areas not claimed by patents. Patent disclosures can guide rival firms' efforts to "design-around" patents, so that they can develop non-infringing products to compete with the patented discovery and thus spur greater innovation.¹¹⁶

Patent protection also covers several components of biotechnology products, including claims drawn to:¹¹⁷

- the compound or molecule,
- methods of treatment (specific indications, route of administration),
- formulation and dosage form,
- product-by-process claims (products defined by the process used to make the molecule),
- manufacturing process (including cell lines used in the manufacturing process), and
- manufacturing technology (technology platforms and research tools used to make the molecule).

With one key difference, these are the same types of patent claims that claim small-molecule products. Process patents and technology platform patents are often more important for biologic drug products than for small-molecule drug products. Process patent claims are important because the "processes by which biologics are made are highly specific, complex, and determine many of the biologic's functional and structural characteristics. . . [that] can often be expected to affect the product's safety, purity, and efficacy profile, and thus are integral to the approval of the product itself."¹¹⁸ Process claims, therefore, add a layer of patent protection that small-molecule drug products may not possess.¹¹⁹

¹¹⁶ *Id.* at 1-2.

¹¹⁷ See BIO Comment (9/30/08) at 10-12.

¹¹⁸ BIO Comment (9/30/08) at 12; see also Bruce S. Manheim *et al.*, *'Follow-On Biologics': Ensuring Continued Innovation In The Biotechnology Industry*, 25 HEALTH AFFAIRS 2: 394-404, 397(March/April 2006) ("the identity of a [biologic] product is clearly dependent upon the process used to manufacture the product.").

¹¹⁹ One commenter noted that not all biologic manufacturing processes are patented, and may restrain entry by FOBs because they are trade secrets in the possession of the branded manufacturers. Essential Action Comment (12/22/08) at 3, and fn. 3 (quoting Gregory Mandel, *The Generics Biologics Debate: Industry's Unintended Admission That Biotech Patents Fail Enablement*, 11 Va. J.L. & Tech. at 66 (2006)). Trade secrets often cover methods of making biologic products. See e.g., Letter from Director Steven K. Glason, FDA Center for Evaluation and Research ("CDER") to Petitioners (May 30, 2006) at 9, available at <http://www.fda.gov/ohrms/dockets/dockets/04P0231/04P-0231-pdn0001.pdf> [hereinafter "FDA's Second

Indeed, concern previously centered on the belief that biotechnology patent protection was too strong because of patent claims covering research tools used to assist in the drug discovery process. The concern was that patented research tools would actually obstruct commercialization of new products, thereby hindering follow-on innovation.¹²⁰ This problem has yet to materialize.¹²¹

C. Patent Protection in the Biotechnology Industry

The introduction of FOB competition raises the question of whether pioneer biologic drug products should be granted an exclusivity period to incentivize innovation. This section summarizes the two competing arguments regarding the strength of patents to continue to incentivize biotechnology R&D in the face of FOB competition.

1. Panelists' and Commenters' Arguments that Patents Are Unlikely to Incentivize Innovation in Light of FOB Competition

Panelists and commenters representing pioneer biologic drug manufacturers suggested that biologic drug patents are likely to provide less investment certainty than patents claiming small-molecule drug products because FOB products are likely to be similar to, not exact duplicates of, the branded drug product.¹²² The panelists suggested that FOB competitors could develop biosimilar products by designing around the branded product's patents.¹²³

Response to Omnitrope CPs"; Reinhardt Comment (10/19/08) at 2; Novartis Comment (9/29/08) at 2; Momena Comment (9/30/08) at 40.

¹²⁰ FTC PATENT REPORT, at Ch. 3 at 1; Michael Heller *et al.*, *Can Patents Deter Innovation? The Anticommons in Biomedical Research*, 280 SCIENCE at 698-701 (MAY 1, 1998) (posits the concern that while biomedical patents spur private investment to support innovation but risks paradoxically the proliferation of fragmented and overlapping intellectual property rights which may restrict the number of commercialized products for improving human health); Suzanne Scotchmer, *Standing On The Shoulders Of Giants: Cumulative Research And Patent Law*, JOURNAL OF ECONOMIC PERSPECTIVES, 5 AMERICAN ECONOMIC ASSOCIATION 1: 29-41 (1991); see also HHS, NIH, *Principles and Guidelines for Sharing of Biomedical Resources*, 64 Fed. Reg. No. 246, 72090 (December 23, 1999) (ensuring that the conditions imposed on the transfer of research tools will facilitate further biomedical research, consistent with the requirements of the Bayh-Dole Act).

¹²¹ John Walsh *et al.*, *Effects of Research Tools Patents and Licensing on Biomedical Innovation*, PATENTS IN THE KNOWLEDGE BASED ECONOMY, 285-336 (2003); John Walsh *et al.*, *View From the Bench: Patents and Material Transfers*, 309 SCIENCE 2003-03 (September 23, 2005); Office of Industries, U.S. International Trade Comm'n, *Patenting Trends and Innovation in Industrial Biotechnology* (October 2008).

¹²² See, e.g., AEI Comment (12/10/08) at 5 ("[D]ata exclusivity is a tool that comes into play when patents fail to provide reasonable protection for innovation."); BIO Comment (9/30/08) at 4; Duke University Comment (12/22/08) at 3.

¹²³ Norman at 156.

A commenter predicted that the pioneer drug manufacturer does not know whether its patent estate is going to cover the exact molecule that an FOB manufacturer produces.¹²⁴ Another commenter summed up this difficulty by suggesting that “the uncertain ‘similarity’ standard for approval of FOBs creates a greater potential for biologic patents to be designed around, particularly given some of the available case law involving the scope of biologic patents.”¹²⁵

Panelists and commenters also suggested that the uncertain scope of patent protection was caused by recent rules of the U.S. Patent and Trademark Office (PTO) and Federal Circuit decisions narrowing of the claims to the biologic molecule.¹²⁶ A panelist suggested that Federal Circuit decisions and PTO practices have forced patentees to obtain “snapshot” claims that limit the claim scope of the compound patent to the exact amino acid sequence.¹²⁷ A panelist suggested that in light of these developments, the PTO is applying the written description requirements in such a way that “it is very difficult to get any kind of scope.”¹²⁸ Another panelist noted that for biologics, it is much more difficult to establish claims drawn to a broad genus that support current written description and enablement requirements.¹²⁹ Additionally, one panelist explained that the PTO recently issued written description guidelines supporting a more narrow interpretation of the written description requirement such that a greater percentage of homology is required in molecules patent claims covering DNA sequences.¹³⁰

Some panelists also discussed the market effects from the Federal Circuit’s decisions scaling back the doctrine of equivalents -- a doctrine that allows for a finding of infringement when the infringing product does not fall within the literal scope of the patent claim but is equivalent to the claimed invention.¹³¹ Panelists and commenters suggested that the practical effect of these current trends in patent law portends difficulty for a branded firm to broaden the scope of its patent claims to cover all equivalent products, especially if the biosimilar differs from the branded biologic by a small variation in amino acid sequences.

¹²⁴ Kushan at 180.

¹²⁵ Manspeizer at 148-49; BIO Comment (12/22/08) at 5; *see also* Wyeth Comment (12/18/08) at 8..

¹²⁶ *See e.g.*, Wyeth Comment (12/18/08) at 8; Manheim, *Follow-On Biologics*.

¹²⁷ Seide at 150-52; BIO Comment (12/22/08) at 5-6 (citing case law).

¹²⁸ Kepplinger at 158-59 (further explaining that under the PTO’s current practice for a molecule patent claim to a method of use or function, the PTO will restrict the function claim to the narrow molecule and not broaden it across variations of that molecule.)

¹²⁹ Dow at 166-67.

¹³⁰ Kepplinger at 157-58; *see generally* Patent and Trademark Office, Written Description Training Materials (2008), available at <http://www.uspto.gov/web/menu/written.pdf>.

¹³¹ *See* Goldman at 164-65, Kepplinger at 158-59; Manspeizer at 148-49.

Another panelist described that when a patent applicant narrows claims during the patent prosecution at the PTO, it has the collateral effect under prosecution history estoppel of surrendering future claims under the doctrine of equivalents that the patentee might try to claim against a biosimilar entrant.¹³²

2. Panelists' and Commenters' Arguments that Patent Protection Provides Ample Incentives for Innovation

FOB manufacturers suggested that these arguments were overbroad because of the number and scope of patents that pioneer manufacturers control relating to their biologic products. For example, FOB commenters and panelists explained how the molecule patents claiming branded products would likely be infringed by FOBs.¹³³ Thus, a "minor and immaterial sequence change is very likely to expose a follow-on biologic to an infringement risk."¹³⁴ Another commenter explained that while "smaller biopharma products (such as peptides, fragments and small proteins) may have granted patents covering the full sequence of the product, Amgen's recent success on EPO full sequence claims against Roche and Transkaryotic Therapies (different products and technologies) shows the power in such claims."¹³⁵

Some FOB manufacturers suggested that process patents will likely provide additional protection against infringing products, making it more difficult for FOB manufacturers to design around the patents and obtain FDA approval of an FOB product.¹³⁶ For example, one panelist suggested that the pioneer manufacturer may have patented the most commercially viable manufacturing methods and the FOB industry may not be able to devise "another commercially appropriate way to circumvent a process patent."¹³⁷ In light of this problem, another commenter suggested that process "patents often provide a level of market protection because the biological origin of their discovery makes them necessary for a production of a product."¹³⁸

¹³² Dow at 166-67, 169; Manspeizer at 148-49.

¹³³ Hospira (Wilkie Farr) Comment (12/22/08) at 2 ("Biologics are large molecules, and product patents typically only claim their 'active' regions. [footnote omitted] These active regions engage the molecule with its surrounding environment and create the therapeutic effect. Thus, while biosimilars might be similar, but not identical, their functionality will likely require resolution of product claims covering the biologic's active region, regions that will often be shared by both the reference biologic and the biosimilar."); Leicher at 161-62; Winston & Strawn ("W&S") Comment (12/22/08) at 4.

¹³⁴ Pearce at 169.

¹³⁵ Hospira (Wilkie Farr) Comment (12/22/08) at 3; *Amgen, Inc. v. F. Hoffmann-La Roche Ltd.*, 2008 U.S. Dist. LEXIS 77343 at * 13 (D. Mass. Oct. 2, 2008); *Genzyme Corp. v. Transkaryotic Therapies, Inc.*, 346 F.3d 1094 (Fed. Cir. 2003).

¹³⁶ Hospira (Wilkie Farr) Comment (12/22/08) at 2.

¹³⁷ Pearce at 144-45.

¹³⁸ Momenta Comment (12/22/08) at 8.

Another commenter suggested that additional barriers to FOB entry are created by well-known platform technology patents used in the research, development and manufacture of biopharmaceutical products.¹³⁹ This commenter explained that “[t]hese patents are extremely broad and tend to overlap with one another, providing brand biopharmaceuticals with wide-ranging protection over their drug products.”¹⁴⁰

FOB manufacturers suggested that “[b]iologic patents are more likely to obtain patent term extensions under Section 156 [of the Patent Act] due to the long and complex patent prosecutions.”¹⁴¹ These extensions ebb and flow with the PTO’s workload.¹⁴² FOB manufacturers also suggested that biologics “are also more likely than chemical drugs to be covered by ‘submarine’ patents.”¹⁴³

D. Patent Protection is Likely to Continue to Provide Strong Incentives for Innovation after Introduction of Follow-On Drug Competition

The patent system has a proven record of protecting and stimulating biotechnology innovation.¹⁴⁴ The introduction of FOB drug products does not alter the relationship of pioneer biologic drug products to the patents protecting them. Pioneer biologic drugs are covered by more and varied patents than small-molecule branded

¹³⁹ Panelists explained the number of patents per biologic product, including platform patents, is substantial, resulting in significant “stacking” of patents (or royalties) compared to the small-molecule patent estates. See Dow at 185; Sauer at 261; Seide at 238; Duncan Bucknell Co. Comment (1/9/09) at 9; Momenta Comment (9/30/08) at 6-7; Wyeth Comment (9/30/08) at 4.

¹⁴⁰ Essential Action Comment (12/22/08) at 3, and fn. 3 (quoting Gregory Mandel, *The Generics Biologics Debate: Industry’s Unintended Admission That Biotech Patents Fail Enablement*, 11 Va. J.L. & Tech. at 66 (2006)); W&S Comment (12/22/08) at 5;.

¹⁴¹ W&S Comment (12/22/08) at 3.

¹⁴² Leicher at 162-63; Dow at 185.

¹⁴³ Hospira (Wilkie Farr) Comment (12/22/08) at 3. Submarine patents result from older patent applications that are not published. Because the applications are not made available 18 months after filing, competitors cannot use the applications to determine whether their FOB products in R&D are likely to infringe potential issued patents. This also creates uncertainty for competitors.

¹⁴⁴ F.M. Scherer & David Ross, *INDUSTRIAL MARKET STRUCTURE AND ECONOMIC PERFORMANCE*, at 621 (3rd Ed., 1990); see also *Patent Reform: The Future of American Innovation, Hearing Before the S. Comm. on the Judiciary*, 110th Cong. (2007) (statement of Kathryn L. Biberstein, Senior Vice President, Alkermes) at 2; *Patent Reform Act of 2007: Hearing on H.R. 1908 Before the H. Subcomm. on Courts, the Internet, and Intellectual Property of the H. Comm. on Judiciary*, 110th Cong. 65 (2007) (statement of Kevin Sharer, CEO of Amgen), available at <http://judiciary.house.gov/hearings/April2007/Sharer070426.pdf>; *Stifling or Stimulating - The Role of Gene Patents in Research and Genetic Testing Before the H. Comm. on the Judiciary, Subcomm. on Courts, the Internet, and Intellectual Property*, 110th Cong. (2007) (statement of Jeffrey P. Kushan on Behalf of BIO), available at <http://judiciary.house.gov/hearings/pdf/Kushan071030.pdf>.

products, including manufacturing and technology platform patents.¹⁴⁵ Patent cases between pioneer manufacturers reveal that patents such as process, manufacturing, and method of use claims can be infringed by a branded competitor.¹⁴⁶ These cases show that the range of patents claiming a biologic product provide a strong assurance that at least one of a biologic drug product's patents will cover an FOB drug product.

There is no evidence that the patents claiming the compound or molecule of pioneer biologic drugs have been designed around more frequently than those claiming small-molecule drug products. There are a variety of ways to draft claims broadly enough to cover the types of drug structure variations expected in follow-on biologics.¹⁴⁷ For example, patent claims reciting the amino acid sequence of a biologic drug compound or molecule can encompass not only the specific sequence, but also a broad genus of structurally and/or functionally related variants through the use of "percent identity claims." An example of a percent identity claim would be "a protein comprising an amino acid sequence sharing at least 70% identity with the described amino acid sequence."¹⁴⁸ The PTO's Written Description Guidelines specifically allow the use of percent identity claims.¹⁴⁹ The effect of these claims is that the patent covering the pioneer biologic drug can be broader than the actual product.¹⁵⁰ Using the example

¹⁴⁵ *Id.*, see also Dow at 185; Sauer at 261; Seide at 238; Duncan Bucknell Co. Comment (1/9/09) at 9; Momenta Comment (9/30/08) at 6-7; Wyeth Comment (9/30/08) at 4.

¹⁴⁶ Bio-Technology Gen. Corp. v. Genentech, Inc., 267 F.3d 1325, 1333 (Fed. Cir. 2001) (reversing trial court's finding of invalidity for lack of enablement regarding method of production patent); see also Press Release, Genentech, Genentech Receives Final Notification Upholding Cabilly Patent in Reexamination Proceeding (Feb. 24, 2009), available at www.gene.com (announcing PTO issuance of Notice of Intent to Issue a Reexamination Certificate confirming patentability of all claims of the Cabilly Patent (U.S. Pat. No. 6,331,415) claiming methods of making recombinant cells expressing both an immunoglobulin light chain and heavy chain used in genetically-engineered monoclonal antibodies).

¹⁴⁷ John R. Thomas, *Toward a Theory of Marketing Exclusivities* at 32-33 (2009) (forthcoming) ("Biotechnology products may commonly be defined through multiple techniques, including their structure, chemical or physical characteristics, and method of preparation, that in combination are capable of providing a potent shield against would-be competitors.").

¹⁴⁸ Christopher M. Holman, *Is Lilly Written Description a Paper Tiger?: A Comprehensive Assessment of the Impact of Eli Lilly and Its Progeny in the Courts and PTO*, 17 ALB. L.J. SCI. & TECH. 1, 44 (2007).

¹⁴⁹ PTO, WRITTEN DESCRIPTION TRAINING MATERIALS (2008), available at <http://www.uspto.gov/web/menu/written.pdf>.

¹⁵⁰ See, e.g., *Infigen, Inc. v. Advanced Cell Technology, Inc.*, 65 F. Supp.2d 967,975 (W.D. Wis. 1999) ("It is black letter law that claims are not limited to the embodiment described in the patent specifications. Moreover, a patent claim may encompass uses not anticipated by the inventor and therefore not described in the patent.") (citations omitted). This principle extends beyond percent identity claims. *Capon v. Eshhar*, 418 F.3d 1349, 1359 (Fed. Cir. 2005) (reversing BPAI interpretation of written description and holding, "It is not necessary that every permutation within a generally operable invention be effective in order for an inventor to obtain a generic claim, provided that the effect is sufficiently demonstrated to characterize a generic invention."); *Invitrogen Corp. v. Clontech Labs.*, 429 F. 3d 1052, 1071-74 (Fed. Cir. 2005) (holding that disclosure of a known protein variant satisfied written description for claims encompassing engineered protein variants with shared function); *id.* at 1073 ("Enablement does not require the inventor to foresee every means of implementing an invention at pains of losing his patent franchise."),

above, an FOB drug product's molecule could differ by up to 30 percent and still infringe the patent protecting the pioneer product.¹⁵¹

The scope of drug compound or molecule patents depends on the claim language and patent prosecution. Although it is true that alleged competitors have been found not to infringe drug compound claims because of the way in which the claims were construed,¹⁵² it is equally true that biotechnology drug product claims have been construed so that accused products have been found to infringe even when they have varied from the patentee's corresponding product.¹⁵³ For example, a pioneer manufacturer recently obtained a permanent injunction after a finding that its patents were infringed by a competitor that had altered the patented molecule slightly.¹⁵⁴ Other cases are pending as well.¹⁵⁵

see generally Christopher M. Holman, *Is Lilly Written Description a Paper Tiger?: A Comprehensive Assessment of the Impact of Eli Lilly and Its Progeny in the Courts and PTO*, 17 ALB. L.J. SCI. & TECH. 1 (2007) (a comprehensive review of federal court and PTO Board of Patent Appeals and Interferences decisions reveals no support for the proposition that since the Lilly decision, which purportedly tightened the written description requirements for biotechnology drug molecule claims, patentees have not been able to obtain patents with sufficiently broad scope.).

¹⁵¹ Christopher M. Holman, *Is Lilly Written Description a Paper Tiger?: A Comprehensive Assessment of the Impact of Eli Lilly and Its Progeny in the Courts and PTO*, 17 ALB. L.J. SCI. & TECH. 1, 47 (2007).

¹⁵² *Biogen, Inc. v. Berlex Labs*, 318 F.3d 1132, 1140-42 (Fed. Cir. 2003) (affirming trial court's finding that there was no literal infringement and vacating summary judgment of non-infringement under the doctrine of equivalents); *Genentech, Inc. v. The Wellcome Found. Ltd.*, 29 F.3d 1555, 1569 (Fed. Cir. 1997) (reversing trial court's denial of defendant's JMOL in part because an element of the doctrine of equivalents was not met); *Novo Nordisk of N. America, Inc., v. Genentech, Inc.*, 77 F.3d 1364, 1367-71 (Fed. Cir. 1996) (vacating preliminary injunction on grounds that district court erred in finding literal infringement where "direct expression" of human growth hormone did not cover alleged infringers "cleavable fusion" process for producing the hormone); *Hormone Research Foundation, Inc., v. Genentech, Inc.*, 904 F.2d 1558, 1563-67 (Fed. Cir. 1990) (finding no literal infringement, vacating infringement under the doctrine of equivalents, holding that the patentee did not intend "corresponding to" and "similar" to have the same meaning, and ruling that "corresponding to" reflected true identity).

¹⁵³ *Genentech, Inc. v. Chiron Corp.*, 112 F.3d 495, 501 (Fed. Cir. 1997) (reversing district court's claim interpretation in interference proceeding because it was "not the broadest, reasonable interpretation of the count.") (citing *Genentech, Inc. v. The Wellcome Found., Ltd.*, 29 F.3d 1555 (Fed. Cir. 1997)); *Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1219 (Fed. Cir. 1991) (affirming trial court's finding that certain claims covering purified and isolated DNA sequences encoding EPO and host cells transformed or transfected with a DNA sequence were valid and infringed and reversing finding that other claims were enabled); *Amgen, Inc. v. Hoffmann-LaRoche Ltd.*, 2008 U.S. Dist. LEXIS 77343 (D. Mass. 2008) (granting permanent injunction for infringement of claims directed to a specific amino acid sequence); see also *Amgen Inc. v. Hoechst Marion Roussel*, 579 F. Supp. 2d 199, 210 (D. Mass. 2008); *Chiron v. Genentech, Inc.*, 268 F. Supp. 2d 1126, 1138 (E.D. Cal. 2008); *Genentech, Inc. v. Insmid Inc.*, 436 F. Supp. 2d 1080, 1091-92 (N.D. Cal. 2006) (granting patent holder's partial motion for summary judgment and finding literal infringement of a patent claiming "Preparation of Human IGF via Recombinant DNA Technology").

¹⁵⁴ *Amgen, Inc. v. F. Hoffmann La Roche, Ltd.*, 2008 U.S. Dist. LEXIS 77343 (D. Mass. Oct. 2, 2008).

¹⁵⁵ See e.g., *Bayer HealthCare LLC v. Abbott Laboratories*, Civ. Action No. 6:08cv507 (E.D. Tex. Dec. 24, 2008), complaint available at <http://www.patentbaristas.com/wp/wp-content/uploads/2009/01/bayer.pdf>.

To the extent an FOB manufacturer will attempt to design around a pioneer manufacturer's patent, that effort is to be expected and encouraged. Competing branded manufacturers have been doing just that since the early days of biotechnology patents.¹⁵⁶ The purpose of the required patent disclosures is to assist rival firms to design around patents so that they can develop non-infringing products to compete with the patented discovery and thus spur greater innovation.¹⁵⁷ Of course, FOB manufacturers run the risk that the more their drug molecule differs from the pioneer product's molecule to avoid patent infringement issues, the greater the chance that its product will no longer be "similar" enough to the pioneer product to use the FOB approval process.

Finally, even if the FOB manufacturer were to design around the patents claiming a pioneer biologic drug product and enter prior to patent expiration, the pioneer manufacturer will continue to earn significant revenues after FOB entry. Pioneer manufacturers are likely to retain 70 to 90 percent market share following FOB entry. Moreover, the overall market is likely to expand following FOB entry, thereby diminishing the loss of revenue by the pioneer manufacturer. The effect on the pioneer manufacturer caused by FOB entry is not nearly as great as it is with small-molecule generic drug entry.

In sum, continued reliance on the patent system to stimulate biotechnology innovation is well-justified. This reliance is well-placed especially if the FOB abbreviated FDA drug approval process does not contain special regulatory features similar to the ones in Hatch-Waxman that incentivize patent challenges prior to FDA approval of the FOB drug and undermine the ability of the patent to incentivize innovation.

Abbott countersued in Massachusetts: *Abbott Laboratories v. Bayer Healthcare LLC*, 09cv40002, U.S. District Court for the District of Massachusetts, 09cv40002, (D. Mass. June 5, 2008).

¹⁵⁶ BIO Comment (9/30/08) at 22 (citing industry experience over more than two decades of biotechnology patent litigation).

¹⁵⁷ FTC PATENT REPORT, Ch. 3 at 1-2.

III. OTHER CONSIDERATIONS DO NOT SUPPORT A 12- TO 14-YEAR BRANDED EXCLUSIVITY PERIOD

Commenters and panelists also described the need for, and the likely effects of, a 12- to 14-year branded exclusivity period. The next two sections summarize these views and the need for a 12- to 14-year exclusivity period. The third section provides an analysis of these effects.

A. Panelists' and Commenters' Views on the Likely Effects of a Branded Exclusivity Period

Pioneer manufacturers suggested that a 12- to 14-year branded exclusivity period provides certainty about recoupment when R&D investment decisions are made.¹⁵⁸ Moreover, exclusivity only protects the pioneer manufacturer from the use of its own data by a potential FOB competitor for the length of the exclusivity period.¹⁵⁹

To calculate the recoupment amount, pioneer manufacturers rely on an economic model (the "Nature model") that calculates the time it takes for a manufacturer to recover fully its investment to develop and commercialize a typical biologic drug.¹⁶⁰ Some commenters have concluded that the Nature model supports a branded exclusivity period between 12.9 and 16.2 years in length.¹⁶¹

Pioneer manufacturers suggested that a branded exclusivity period substantially shorter than 14 years would be disastrous for innovation and patients.¹⁶² They suggested that without substantial exclusivity, there will be a decrease in the number of "targets of opportunity" for which FOBs could reference.¹⁶³ In addition, R&D would shift away from new treatments for diseases, thus depriving the public of much needed treatments

¹⁵⁸ Phillips at 100-01 ("[I]f there is no chance to recoup the capital outlay, then the investment won't be made."). This panelist also suggested that there is a dynamic effect to a branded exclusivity period in that it "is going to change the status quo for investment decisions made by innovator companies;" *see also* AEI Comment (12/10/08); Eli Lilly Comment (12/19/08) at 2; Wyeth Comment (12/18/08) at 2 ("Just as certainty spurs innovation and advances that benefit patients, lack of certainty in the pharmaceutical and biotechnology industries hinders innovation").

¹⁵⁹ Johnson & Johnson Comment (3/17/09) at 6.

¹⁶⁰ Grabowski, *Follow-on Biologic*.

¹⁶¹ Duke University Comment (12/22/08); PhRMA Comment (12/22/08).

¹⁶² *See, e.g.*, BIO Comment (9/30/08) at 17 ("Failure to provide substantial data exclusivity would fundamentally alter the ability of biotechnology companies to continue to innovate because these companies, in order to secure the necessary resources from venture capital firms and other funding sources, must have some certainty that they can prevent free-riding on their investment in the development of new breakthrough therapies for a substantial period of time.")

¹⁶³ Wyeth Comment (12/18/08) at 10.

for unmet medical needs, toward ‘safer’ bets such as new formulations or second generation molecules.”¹⁶⁴

Others suggested that a branded exclusivity period should be similar to the actual amount of time that patented small-molecule products enjoy before generic entry occurs.¹⁶⁵ Under Hatch-Waxman, even though the maximum amount of branded exclusivity is five years, generic entry occurs, on average and depending upon the size of the market, between 11 and 13 years after FDA approval of the branded drug product.¹⁶⁶

Although one panelist questioned why, if the exclusivity period were short, the pioneer manufacturer could not raise prices to make up for any shortfall in revenue and thus not be any worse off.¹⁶⁷ However, another panelist explained that the “the key driver of prices will be if you’re in a market where there’s competition or anticipated competition.”¹⁶⁸

By contrast, commenters representing FOB manufacturers suggested that experience under Hatch-Waxman informed their view that a long exclusivity period would lengthen the time between innovations and do little to stimulate innovation. Instead, a 14-year branded exclusivity period may simply reduce the pace of innovation.¹⁶⁹ One commenter predicted that if the branded exclusivity period were that long then branded manufacturers would engage in minor product enhancement strategies which would multiply the costs of expanding monopoly protection.¹⁷⁰ Others noted that long exclusivity periods will eliminate or substantially delay the efforts by FOB manufacturers in making innovations in safety, convenience, cost, access, immunogenicity, interchangeability, or new indications for biologics.¹⁷¹

¹⁶⁴ *Id.* at 9.

¹⁶⁵ BIO Comment (12/22/08) at 6.

¹⁶⁶ Henry Grabowski *et al.*, *Generic Competition and Market Exclusivity Periods in Pharmaceuticals*, *MANAGERIAL AND DECISION ECONOMICS* 28 (2007) 491–502, at 493 (the study examined 251 products that encountered generic entry between 1995 and 2005).

¹⁶⁷ Heldman at 117; *see also* Essential Action Comment (12/22/08) at 2 (“[F]ree from competitive pressures they can set a price that allows them to earn profits, and not just recoup their R&D costs.”).

¹⁶⁸ Grabowski at 117-18 (“[P]rice is going to be driven by your interaction with payers and other competitors.”).

¹⁶⁹ Zuckerman Spaeder Comment (12/22/08) at 12.

¹⁷⁰ Teva Comment at 5 (“Evergreening will multiply the economic costs of expanding monopoly protection via exclusivity arrangements. Brand companies can, and routinely do, make relatively minor changes to their existing products in order to restart their monopoly-protection clocks.”).

¹⁷¹ Brugger at 74; Behrman at 77-79; Grabowski at 80; Barr Comment (12/19/08) at 1-2 (the anticompetitive barrier to FOB competition is longer than just the term of the exclusivity period, as FOB cannot file its application until the day after the period expires, and entry is further delayed for year(s) while FDA reviews the FOB’s application.); Momenta Comment (12/22/08) at 1-3; Novartis Comment (9/29/08) at 10 (“With no market access, there is only limited incentive to make safe and effective

B. Panelists' and Commenters' Views on the Need for Branded Exclusivity to Incentivize Incremental Innovation

The panelists and commenters also examined how the existence and length of an exclusivity period could affect incremental innovation. Pioneer manufacturers explained that there likely would not be incremental innovation without recoupment to recover these investments.¹⁷² In this context, participants used the term “incremental innovation” to refer to actions such as the discovery of a new indication for a previously approved product, or an improved formulation for greater safety or convenience.¹⁷³

A commenter suggested that a 12- to 14- year period of exclusivity is necessary to encourage post-FDA approval research. This commenter explained “that at the time a novel biologic is approved, little may be known of what that drug can do or of what can be achieved in connection with its biological target.”¹⁷⁴ Another commenter suggested that without an additional exclusivity period the number of post-approval clinical trials testing new uses of already approved biologic would drastically decrease due to the lack of certainty of an adequate return on investment. For example, instead of anti-cancer biologics being tested in a dozen or more indications in large scale, “Phase IV” clinical trials, no attempt would be made to broaden the use of approved biologic drugs.¹⁷⁵

Another commenter explained that some extension of exclusivity for the pioneer product is necessary to effectively incentivize the development of new indications for, or other improvements to, existing products. Without such an extension, this commenter predicted that “healthcare practitioners may decide to use the FOB to treat the new indication regardless of whether the FOB was approved for that indication.”¹⁷⁶

Another panelist suggested, however, that there likely would be a trade-off between the length of the initial branded exclusivity period and additional grants of exclusivity for new indications. He suggested that if additional branded exclusivity is granted, that the initial period be kept shorter to encourage the pioneer manufacturer to engage in the post-approval R&D.¹⁷⁷

competing products . . . expand the market with new indications . . . implement more efficient and cost-effective manufacturing that potentially can enable reductions in costs of goods.”).

¹⁷² Grabowski at 128; Horton at 129-30; Philips at 132-33.

¹⁷³ See John E. Calfee, *Facing Reality on Follow-On Biologics*, AEI (2007), available at http://www.aei.org/docLib/20070423_200704AHPOg.pdf.

¹⁷⁴ AEI Comment (12/10/08) at 2.

¹⁷⁵ Wyeth Comment (12/18/08) at 9.

¹⁷⁶ BIO Comment (12/22/08) at 7-8.

¹⁷⁷ Brill at 133-34.

C. Likely Competitive Effects of a Branded Exclusivity Period

1. The Innovation Benefits of FOB Competition

As discussed in Chapter 1, FOB manufacturers are likely to seek approval of biosimilar products whose market effects are likely to resemble those of pioneer biologic products rather than small-molecule generic products. Innovation benefits due to branded competition include a race among firms attacking an unmet medical need or investigating a promising therapy that results in increased dissemination of scientific knowledge, and a greater chance of developing a breakthrough product to benefit consumers.¹⁷⁸ The social value of the cumulative effects of incremental innovations can often exceed those of the original breakthrough.¹⁷⁹ These same benefits are likely with entry of FOB products.

Branded competitors also enhance their products to differentiate them from their competitors. This is a common dynamic in competitive markets. Automatic substitution of generic drugs distorts this product enhancement dynamic such that branded manufacturers are incentivized to change their products in minor ways to defeat automatic substitution.¹⁸⁰ These minor changes may not provide clinical or patient benefit. The lack of automatic substitution of FOB products, however, is likely to lessen this distortion in biologic drug markets.

2. Actual Pioneer Drug Manufacturer Exclusivity Can Inform the Length of a Branded Exclusivity Period

The head start that first-in-class branded products already experience against second-in-class products can inform the length of a branded exclusivity period for biologics. A subsequent branded competitor obtains limited benefits from the regulatory approval occasioned by the first-in-class product because its R&D efforts have been proceeding on a parallel path with those of the first-in-class manufacturer.¹⁸¹ The head start of the first-in-class drug product has decreased over the last three decades as the average lead time of the first-in-class product shrank from 8.2 years during the 1970s to 2.25 years in the 1990s. This limited period of exclusivity for the first-in-class drug

¹⁷⁸ See generally DiMasi, *The Economics of Follow-on Drug Research and Development*; Ian Cockburn, *The Changing Structure of the Pharmaceutical Industry*, 23 HEALTH AFF. 1:10-22 (2004).

¹⁷⁹ William J. Bauomol, *THE FREE-MARKET INNOVATION MACHINE: ANALYZING THE GROWTH MIRACLE OF CAPITALISM* (2002) at 33 (capitalism benefits society not just through price competition but also through systematic innovation races among all firms in an innovating industry as they vie for consumers and dare not fall behind the others in new products and processes).

¹⁸⁰ See *Abbott Labs. v. Teva Pharm. USA, Inc.*, 432 F. Supp. 2d 408, 413 n.1 (D. Del. 2006) for an example of litigation alleging this type of strategy. See also Herbert Hovencamp, Mark D. Janis & Mark A. Lemley, *IP AND ANTITRUST*, § 12.5 (2006).

¹⁸¹ See generally DiMasi, *The Economics of Follow-on Drug Research and Development*. Although this study examined pharmaceutical products primarily, it included several biologic drugs as well.

product has not dampened R&D incentives and may, in fact, be optimal for rewarding past innovation while allowing competition to incentivize future innovation.¹⁸²

3. FOB Entry is Unlikely to Occur Immediately upon Expiration of a Limited Period of Branded Exclusivity

It is likely that few, if any, biologic products will experience FOB entry immediately upon expiration of a limited period of exclusivity. The generic drug approval process under Hatch-Waxman results in branded manufacturers enjoying approximately 11 to 13 years of *de facto* exclusivity prior to a generic drug entry.¹⁸³ This length of market exclusivity occurs despite the incentives within Hatch-Waxman for generic manufacturers to challenge branded patents prior to FDA approval of the generic drug. Indeed, this length of time is attributable mainly to patent protection and patent restoration.¹⁸⁴

An approach that does not provide incentives to challenge a pioneer product's patents prior to FDA approval is likely to result in a longer period of *de facto* exclusivity than that which occurs under Hatch-Waxman for small-molecule drugs. To the extent patents are at issue, they would be resolved after any branded exclusivity period had expired and FDA approval had been acquired, similar to the way in which branded competitors currently resolve their patent disputes. It is unlikely that FOB manufacturers will expend the substantial resources to develop a biosimilar product and obtain FDA approval if it is likely to run afoul of a pioneer product's patents.

Moreover, expiration of a branded exclusivity period does not mean that FDA approval of an FOB will follow soon thereafter. Pioneer manufacturers are likely to use the citizen petition process to raise safety and efficacy concerns about FOBs, which will delay FOB approvals, as occurred with Omnitrope.¹⁸⁵ Additional delays to FDA approvals of FOB applications would likely occur were FDA required to issue guidance documents, including issuing draft guidance documents, soliciting public comments, and finalizing the guidance documents, before accepting or approving any FOB application for a particular class of branded biologic drugs.¹⁸⁶

¹⁸² Scherer, *Markets and Uncertainty*, at 13.

¹⁸³ Grabowski, *Generic Competition and Market Exclusivity Periods in Pharmaceuticals*, at 493.

¹⁸⁴ Charles Clift, *The Value of Patent Term Extensions to the Pharmaceutical Industry in the USA*, 5 J. GEN. MED. 201-208 (Apr. 2008).

¹⁸⁵ Barr Comment (9/30/08) at 12.; PhRMA Comment (9/30/08) at 19 ("As in the case of generic drugs, any regulatory approval pathway for FOBs would involve complex scientific and legal considerations that can and should be raised through appropriate mechanisms, such as citizen petitions. Innovator companies have extensive knowledge about their products, and are often in the best position to bring to FDA's attention complex regulatory and scientific issues regarding appropriate approval standards.").

¹⁸⁶ See, e.g., H. 1548, 111th Cong. § 101(k)(2)(B)(iii) (2009) (guidelines required for assessing immunogenicity); *id.* at § 101(k)(4)(B) (guidelines required for assessing interchangeability); and *id.* at § 101(k)(5)(C) (guidelines required for Risk Evaluation and Mitigations Strategy).

Even if patent litigation were to start following FDA approval, pioneer manufacturers would likely have *de facto* exclusivity for several years after the period ends due to the time it takes to resolve complex patent litigation. The FTC 2002 Generic Drug Study calculated that obtaining a district court resolution of patent issues under the Hatch-Waxman Act took on average 25.5 months and that it took over 12 more months to obtain a court of appeals decision.¹⁸⁷ Given that the patent portfolios for biologic products are likely to include patents owned by third party entities, this time could be substantially extended.¹⁸⁸ Thus, the effect of patent litigation starting after FDA approval of an FOB would delay FOB entry beyond the expiration of a limited branded exclusivity period.

4. Exclusivity Periods Have Been Used When Patent Protection Has Been Insufficient to Incentivize and Reward Innovation

Congress has implemented exclusivity periods to encourage the development of new and innovative drug products when the drug molecule is in the public domain, and therefore not patentable.¹⁸⁹ Similarly, exclusivity periods have been used to incentivize the post-FDA approval clinical trials for new uses of existing drug products. For example, the Hatch-Waxman Act provides a five-year exclusivity period to incentivize the development of new chemical entities. It also provides a three-year exclusivity period for new clinical investigations (“NCI”) of small-molecule drugs.¹⁹⁰

In other instances, Congress has implemented an exclusivity period when market-based pricing has not provided sufficient incentive to develop drug products for target populations. For example, 6-months of marketing exclusivity periods are awarded upon the showing of safety and effectiveness for children. A seven-year marketing exclusivity period is awarded to manufacturers of drug products that treat diseases affecting less than 200,000 persons in the United States.¹⁹¹

¹⁸⁷ See FEDERAL TRADE COMM’N, GENERIC DRUG ENTRY PRIOR TO PATENT EXPIRATION: AN FTC STUDY (JULY 2002), at iii, available at <http://www.ftc.gov/os/2002/07/genericdrugstudy.pdf>.

¹⁸⁸ See *infra* Chapter 3.

¹⁸⁹ See BIO Comment (5/1/09) at 7-9 (Benjamin Roin, *Unpatentable Drugs and the Standards of Patentability* 87 TEX. L. REV. (forthcoming)).

¹⁹⁰ See Appendix B for a description of the marketing exclusivities for small-molecule drug products.

¹⁹¹ See Orphan Drug Act (“ODA”), 21 U.S.C.A. § 360aa *et seq.* (2009), 21 C.F.R. § 316 *et seq.*; FDA, Office of Orphan Products Dev’t, Cong. Findings For the ODA (“[B]ecause so few individuals are affected by any one rare disease or condition, a pharmaceutical company which develops an orphan drug may reasonably expect the drug to generate relatively small sales in comparison to the cost of developing the drug and consequently to incur a financial loss; there is reason to believe that some promising orphan drugs will not be developed unless changes are made in the applicable Federal laws to reduce the costs of developing such drugs and to provide financial incentives to develop such drugs.”) available at <http://www.fda.gov/orphan/oda.htm>. It is likely that the patents for orphan drugs and not the 7-year ODA exclusivity period provide the greatest incentive to innovators. See Robert Rogoyski, *The Orphan Drug*

Central to each of these exclusivities is a public policy trade-off: a restriction on competition is provided in return for a development of a new drug product or new use of an existing product. A 12- to 14-year exclusivity period, however, departs sharply from this basic trade-off, because it does not spur the creation of a new product or indication. The drug has already been incentivized through patent protection and market-based pricing.

To the extent that there are new biologic molecules that cannot obtain patent protection, an exclusivity period may be warranted. Because there is no evidence about the lack of patentability of new biologic products, nor that market forces have been insufficient to incentivize their development, the Commission has not recommended a length of an exclusivity period.

One benefit of an FOB approval process is that it provides an efficient way to advance scientific progress and commercialization of that scientific innovation. An FOB approval process eliminates unnecessary clinical tests and allows competition to generate better consumer products at lower prices. The potential harm posed by a 12- to 14-year exclusivity period is that firms will direct scarce R&D dollars toward developing low-risk clinical and safety data for drug products with previously proven efficacy rather than toward new inventions to address unmet medical needs. Thus, a new 12- to 14-year branded exclusivity period imperils the efficiency benefits of an FOB approval process in the first place.

In addition, a 12- to 14-year branded exclusivity period could undermine the patent system's disclosure function as pioneer manufacturers rely on trade secrets rather than patents to protect their inventions. Because the patent system requires public disclosure, it promotes the dissemination of scientific and technical information that would not occur but for the grant of a patent. The scientific community can then learn and design around the invention. The ability to design around is prevalent for patent claims covering the formulation or dosage of drug products, product-by-process claims, and process claims – all of which currently protect pioneer biologic products. To the extent that the branded exclusivity period replaces the need for the patent, the scientific community loses the disclosure of inventions that occurs when patents are granted and published, and innovation could be harmed.

D. The Nature Model Fails to Inform Reliably the Length of a Branded Exclusivity Period

Pioneer manufacturers have developed the Nature model to show that the optimal length of branded exclusivity should be approximately 14 years. The Nature model, as currently presented, contains numerous methodological and conceptual weaknesses that

Act and the Myth of the Exclusivity Incentive, 7 COLUM. SCI. & TECH. L. REV 2 (2006), <http://www.stlr.org/volumes/volume-vii-2005-2006/rogoyski/>. According to one study, the majority of orphan drugs are protected by patents with both a broader scope than the disorder specific ODA, and a longer duration than the 7-year ODA exclusivity period. *Id.* at 18, Figure 1.

render its results too imprecise and non-robust to inform discussions about the length of an exclusivity period. A model that balances the benefits of FOB competition with the costs of potentially forsaking marginal branded drug development projects would be more informative than the Nature model's approach.¹⁹²

Appendix A further explains and evaluates the assumptions underlying the Nature model. A brief summary of the problems includes:

- **Imprecision:** The estimates of costs and revenues used in the model are based on extremely small samples of drug products and are likely imprecise.
- **Inelastic Demand:** Most versions of the model currently assume that the overall quantity of the drug produced and sold will not expand with FOB entry although they assume that FOB entry will lead to lower prices.
- **Internal Inconsistency:** The ad hoc assumptions about the branded manufacturers' price decrease and market share decline following FOB entry are not necessarily consistent with the likely market dynamics of FOB competition.
- **Excessive Aggregation:**
 - The revenue estimates do not distinguish between the original and subsequent indications and formulations, so an independent analyst cannot modify the framework to calculate the break-even point for just the original indication and formulation.
 - The model is based on a portfolio of biologic drugs that includes blockbuster drugs as well as drugs with relatively less in sales and profit. The use of an average revenue stream likely produces an exclusivity period that overprotects the top-selling drugs which are the only drugs likely to face FOB entry when the branded exclusivity period ends.
- **Non-Robustness:** The model's results are extremely sensitive to small changes in the cost of capital¹⁹³ and other assumptions.

¹⁹² Such an approach would require, at a minimum, R&D cost information to which the FTC does not have access.

¹⁹³ The cost of capital is the annual rate of return that an investor would require. Grabowski, NATURE at 480.

CHAPTER 3 COMPETITIVE EFFECTS OF A PRE-APPROVAL PATENT RESOLUTION PROCESS

I. INTRODUCTION

Patent protection fuels the biotechnology industry's R&D engine.¹⁹⁴ As discussed in Chapter 2, patent protection and market-based pricing enable biotechnology firms to increase their expected profits from investments in R&D, thus fostering innovation that would not occur without patents' exclusionary rights.¹⁹⁵

Special procedures to provide an early start to resolving patent disputes between pioneer and FOB manufacturers prior to FDA approval of the FOB product are unlikely to be successful to facilitate FOB entry. Although special procedures govern patent litigation between branded and generic competitors over small-molecule drug products, these procedures are the exception, not the norm. In every industry, including the biotechnology industry, competing firms have engaged in patent litigation in which the patent holder initiates infringement litigation or the alleged infringer seeks a declaratory judgment of non-infringement or invalidity. In the biotechnology industry, this process usually begins following FDA approval of the competing drug product.¹⁹⁶

The special procedures for small-molecule drugs were designed in 1984 to address the issue of "judgment proof" generic defendants. In this context, the profits of the alleged infringer (the generic entrant) are substantially less than the loss of profits by the branded product manufacturer, because of the substantial price differences between branded and generic products. Consequently, generic entrants in small-molecule drug markets are unlikely to be able to satisfy a potential treble damage award for infringing the branded manufacturer's patents.

This chapter explains that FOB entrants will not be similarly judgment proof. FOB entrants are not expected to offer the deep discounts seen in small-molecule drug competition. Rather, FOB entry is likely to resemble the market impact of entry by subsequent branded entrants. An FOB manufacturer is likely to introduce its FOB product at prices 10 to 30 percent lower than the pioneer manufacturer's price. Because

¹⁹⁴ See *Patent Reform: The Future of American Innovation, Hearing Before S. Judiciary Comm.*, 110th Cong. (2007) (statement of Kathryn L. Bieberstein on behalf of the Biotechnology Organization) ("The biotechnology industry, fueled by the strength of the U.S. patent system, has provided jobs for over 200,000 people in the United States, and has generated hundreds of drug products, medical diagnostic tests, biotech crops, and environmental products."), available at http://judiciary.senate.gov/hearings/testimony.cfm?id=2803&wit_id=6508 [hereinafter, "Bieberstein Statement"].

¹⁹⁵ F.M. Scherer & David Ross, *INDUSTRIAL MARKET STRUCTURE AND ECONOMIC PERFORMANCE*, 621 (3d ed. 1990).

¹⁹⁶ BIO Comment (9/30/08) at 22 ("Biotechnology patent disputes today can be adjudicated within a relatively stable doctrinal framework that is expected to solidify further as biotechnology matures both as a science as an industry.").

FOB entrants will earn greater profits, and will be able to satisfy potential damage awards, the market dynamics of FOB competition do not justify creation of a special regulatory system to protect pioneer manufacturers from judgment-proof defendants.

Although FOB market entry would be eased if an FOB manufacturer had complete certainty as to whether its product infringed the pioneer product's patents, a pre-FDA approval patent resolution process is unlikely to provide greater certainty than use of existing statutory patent resolution mechanisms.¹⁹⁷ A special pre-approval patent resolution process is not likely to succeed in raising and resolving all pertinent patent issues prior to FDA approval. Patents claiming the pioneer product may issue after a pre-approval process has begun and/or after FDA approval. In either situation, the FOB manufacturer will need to resolve these later-issued patents before commercial marketing. The FOB manufacturer's application and product also may change during the approval process such that by starting patent litigation prior to FDA approval would not ensure earlier resolution. Moreover, without a mechanism to enforce the rules of a pre-approval resolution process, there is no guarantee that litigation that is started prior to FDA approval will end earlier. Incorporating a pre-approval patent resolution process into a 12- to 14-year branded exclusivity period is unlikely to mitigate these problems.

Based on the experience under Hatch-Waxman, a pre-approval patent resolution process also is likely to lead to consumer harm, including the facilitation of anticompetitive conduct that defeats the purpose of starting the patent litigation early. In the Hatch-Waxman context, branded manufacturers have used the pre-approval patent regulations to delay generic entry. In addition, generic and branded competitors have entered into "pay-for-delay" patent settlements that delay entry, not encourage it. It is likely that a pre-approval patent resolution process in the FOB context could facilitate collusive agreements and/or provide the pioneer biologic drug manufacturer with competitively sensitive information about a significant potential competitor to which it otherwise would not have access.

¹⁹⁷ To the extent that a pre-approval process is designed to address allegations of poor biotechnology patent quality, these issues may be better addressed in efforts to examine patent reform more broadly. Recent Congressional testimony addressed biotechnology issues in the context of patent reform. See, e.g., *Patent Reform in the 111th Congress: Legislation and Recent Court Decisions: Hearings Before the S. Judiciary Comm.*, 111th Cong. (2009).

II. THE LIKELY EFFECTS OF AN FOB PRE-APPROVAL PATENT RESOLUTION PROCESS

A. Background on the Hatch-Waxman Pre-Approval Patent Resolution Process

Current law exempts the FOB manufacturer from patent infringement liability for work directed towards petitioning the FDA for product approval.¹⁹⁸ To be liable for infringement, an FOB manufacturer must take steps separate and apart from seeking FDA approval, in essence, it must import, make, use, sell, or offer to sell its product.¹⁹⁹ The FOB manufacturer, however, is unlikely to take these steps until it receives FDA approval. Consequently, to have patent litigation begin *before* FDA approval of the FOB, Congress must create an “artificial act of patent infringement” and a mechanism to resolve subsequent patent litigation (a “pre-approval patent resolution process”).

Hatch-Waxman established special procedures to incentivize generic small-molecule drug manufacturers to challenge invalid or narrow patents on branded products. These procedures allowed the patent resolution process to run concurrently with the FDA regulatory approval process. Of course, to the extent a generic applicant seeks entry on the day the last patent claiming the branded drug product expires, these procedures are not utilized.²⁰⁰

To effectuate the pre-approval patent resolution process, Hatch-Waxman requires branded manufacturers to list certain patents claiming the branded drug product in the FDA’s Orange Book. A generic applicant is then required to certify whether it seeks FDA approval prior to the expiration of any of the patents listed in the Orange Book that covers the referenced branded product. If it does, the generic company must provide notice to patent holders and the branded product manufacturer. The notice must include a detailed statement of the factual and legal basis supporting the applicant’s assertion that the listed patents are invalid or not infringed.

To incentivize early pre-approval litigation and resolution, if the branded manufacturer brings infringement litigation within 45 days from notice, the FDA cannot

¹⁹⁸ 35 U.S.C.A. § 271(e)(1) (2009) (“It shall not be an act of infringement to make, use, offer to sell, or sell within the United States or import into the United States a patented invention (other than a new animal drug or veterinary biological product (as those terms are used in the Federal Food, Drug, and Cosmetic Act and the Act of March 4, 1913) which is primarily manufactured using recombinant DNA, recombinant RNA, hybridoma technology, or other processes involving site specific genetic manipulation techniques) solely for uses reasonably related to the development and submission of information under a Federal law which regulates the manufacture, use, or sale of drugs or veterinary biological products.”).

¹⁹⁹ Merck KGaA v. Integra Lifesciences I, Ltd., 545 U.S. 193 (2005).

²⁰⁰ See Appendix B for a description of the patent resolution process in the Hatch-Waxman Act.

approve the generic application for 30 months.²⁰¹ If the branded manufacturer does not initiate litigation within 45 days, the FDA is free to approve the generic application in its normal course.

B. Commenters' and Panelists' Views on the Likely Effects of an FOB Pre-Approval Patent Resolution Process

Panelists and commenters described the likely benefits of developing a pre-approval patent resolution process derived from the Hatch-Waxman Act. Panelists suggested patent infringement certainty would enhance their drug development activities.²⁰² They also suggested that a pre-approval patent resolution process is likely to preclude FOB at-risk launches, which occur when a company launches its product without knowing if all product-related patent issues are resolved.²⁰³ Other panelists predicted that certainty is likely to attract venture capital resources,²⁰⁴ and suggested that smaller companies may not be in a position to launch-at-risk because they are unlikely to attract investment funds without certainty.²⁰⁵ Another panelist predicted that without a pre-approval resolution process, pioneer manufacturers would not be able to enforce injunctive relief against an FOB entrant and that this would lead to compulsory licensing of patents rather than removal of the product from market.²⁰⁶

Panelists and commenters described the likely effects of linking FDA approval to the outcome of patent litigation, as it is done under the Hatch-Waxman Act. Panelists representing pioneer manufacturers explained that if a court finds a pioneer product's patent to be valid and infringed, the FDA should not approve the infringing FOB product until the patent expires.²⁰⁷ Another suggested that tying FDA approval to patent resolution

²⁰¹ This "30-month stay" expires at the earliest of: (1) the date the patent(s) expire; (2) a final determination of non-infringement or patent invalidity by a court in the patent litigation; or (3) the expiration of the 30 months from receipt of notice of the paragraph IV certification.

²⁰² See, e.g., Amgen (9/30/08) Comment at 20 (certainty may increase FOB uptake if physicians are more likely to prescribe an FOB after the product has cleared patent hurdles); Essential Action Comment (12/20/08) at 7 ("should be to clear patent claims so that a) invalid patents do not delay investment in, or introduction of, generic or similar products; b) non-applicable patents do not delay investment in, or introduction of, generic or similar products; and c) all potential patent claims are resolved in advance of any applicable marketing exclusivities."); Manspeizer at 229; Leicher at 232; and Dow at 295-96.

²⁰³ Hospira Comment (9/30/08) at 7 ("Due to the greater uncertainty surrounding the valid scope of patents and the lack of jurisprudence resulting from an immature biopharmaceutical industry as compared to a small molecule drug . . . this will operate as a significant disincentive to launch of a biogeneric and will thus operate as a disincentive to competition."); Seide at 238; and Siwik at 224-25.

²⁰⁴ Amgen Comment (9/30/08) at 20; BIO Comment (9/30/08) at 20.

²⁰⁵ Leicher at 232.

²⁰⁶ Sauer at 227.

²⁰⁷ *Id.* at 271.

would “keep follow-on biologics that infringe a patent off the market by preventing final FDA approval until patent expiry.”²⁰⁸

One panelist and commenter representing a potential FOB entrant suggested that linkage is unnecessary because existing patent law provides for robust protection of patent rights against infringement and is sufficient to deter inappropriate entry.²⁰⁹ This panelist explained that launching-at-risk currently is the norm in the biotech industry.²¹⁰ He also explained that the generic small-molecule industry is the only industry that has an artificial act of infringement, and “that was a result of the state of the industry in 1984, and we don’t believe [it] is required with the state of the industry in 2008.”²¹¹

Another panelist noted that linkage may be unworkable because biologic patent portfolios often include patents that have been licensed to third parties. Infringing one of these patents may not lead to a permanent injunction, and thus should not preclude FDA approval.²¹² Another panelist added that the patent holder may obtain an injunction notwithstanding the fact that they have licensed the patent to other parties.²¹³

Participants also described the likely unintended consequences of a pre-approval patent resolution process, which include: delay of FOB entry, distortions to the parties’ incentives during the process, and increased costs.²¹⁴ For example, one panelist suggested that the process can cause unintended delay, noting that for small-molecule drugs, Hatch-Waxman has led to “serial litigation.”²¹⁵ Another panelist focused on the likelihood of wasteful litigation.²¹⁶

²⁰⁸ Wyeth Comment (9/30/08) at 9; *see also* Wyeth Comment (12/18/08) at 13 (“In order to provide certainty to all parties concerning the outcome of any patent resolution mechanism, a linkage system is required.”).

²⁰⁹ Novartis Comment (9/29/08) at 19; and Goldman at 231 (“Decoupling will avoid premature challenges to biotech patent estates ahead of the prospect of imminent commercialization, and current law provides robust protection for those rights when infringement occurs.”).

²¹⁰ Goldman at 230 (“There’s not a single product that hasn’t come on the market in which launching at risk hasn’t been a key issue. And companies are – all of us here have the ability to take that business risk into consideration and decide whether or not to launch at risk.”); *see also id.* (“[T]he need for an early resolution, early litigation because of the fear of launching at risk is not a serious one we contend.”); and Novartis Comment (9/29/08) at 19.

²¹¹ Goldman at 230-31 (explaining that “[t]here’s no artificial act of infringement in the European scheme as well, so it’s a real aberration.”).

²¹² Siwik at 273-74.

²¹³ Kushan at 276-77.

²¹⁴ Siwik at 224-25 (“[I]t’s important to have a mechanism in the bill for resolving certain patent disputes concurrent with FDA review, but the big but is, if the system doesn’t work, if whatever this patent mechanism is doesn’t work, I guess work in the sense that it can delay market launch.”).

²¹⁵ Goldman at 231 (“You litigate one patent followed by another patent, and that can really extend the litigation pre-approval.”).

Panelists also described how a pre-approval resolution process will distort parties' incentives. One panelist explained that the process will "create bounties on valid patents" by producing an incentive for an FOB to challenge patents before it has shown it can develop an approvable drug.²¹⁷ By starting the process early, that is prior to FDA approval, parties are encouraged to bring multiple litigations, where, if they brought litigation at the end of the process, there may be greater incentive to raise only the strongest patents.²¹⁸ Commenters also explained how if litigation begins too early, the FOB application and product also may change during the approval process such that an early start to litigation prior to FDA approval would not ensure an earlier resolution. Rather, an early start to litigation would lead to additional litigation upon finalization of the application and the FOB product.²¹⁹ Panelists also described how unnecessarily-early litigation processes will increase pioneer and FOB costs, explaining that a pre-approval patent resolution process likely will "bring[] on expensive litigation costs earlier when you might not want to do that."²²⁰

C. Analysis of the Likely Effects of a Pre-Approval Patent Resolution Process

1. The Likely Market Impact of FOB Drug Entry Does Not Warrant a Special Pre-Approval Patent Resolution Process

The justification for special procedures akin to those in Hatch-Waxman for small-molecule drugs depends upon the context in which FOB competition is likely to proceed. As discussed in Chapter 1, FOB competitors are likely to seek approval of biosimilar

²¹⁶ Kepplinger at 267 ("[I]t seems like one of the lessons from Hatch-Waxman, and many people have talked about it, is that there's quite a lot of litigation, and it seems like in designing the situation, we should be looking to try to reduce the litigation because it is just a lot of money that could probably be better spent on other things, like designing more pharmaceuticals.").

²¹⁷ Goldman at 242-43; Novartis Comment (9/29/08) at 18-19.

²¹⁸ Goldman at 231 ("[A]nd besides that, we also see in those cases that there's serial litigation. You litigate one patent followed by another patent, and that can really extend the litigation pre-approval. Post approval, there's no incentive for serial litigation. You would want to bring your best patents quickly to get the product off the market.").

²¹⁹ BIO Comment (9/30/08) at 21 ("Patent litigation would be premature if it were allowed to commence before a determination that the FOB application in question is complete and in condition for review without additional clinical studies."); *see also* Wyeth Comment (12/18/2008) at 13 ("[a] patent resolution proceeding should not be initiated at a point in time that is too early, when the details of the biosimilar product are not yet fully defined or manufacturing processes still are subject to change.").

²²⁰ Goldman at 240-41 ("[I]t surprises me that . . . the companies that are worried about not having enough money are the ones that are advocating jumping into expensive litigation 30 months early. I would think that you would want to avoid that, the litigation [Y]ou may in fact be bringing on expensive litigation costs earlier when you might not want to do that."); *see also* Siwik at 225.

products. The competitive dynamics of biosimilar entry are likely to resemble entry by a branded drug product, in which FOB competitors introduce their products at discounts between 10 and 30 percent of the pioneer products' price. This effect contrasts with the 80 percent discounts that occur with entry of multiple small-molecule generic products.²²¹ The competition prompted by biosimilar entry is unlikely to move more than 10 to 30 percent market share away from the pioneer manufacturer. This market share movement is substantially less than the market share gain that small-molecule generic drugs obtain due to state substitution of generic drugs. Because of smaller discounts and smaller market share, the FOB entrant is unlikely to be judgment-proof and thus able to pay any possible damages resulting from infringing a pioneer product's patents.

Because FOB entrants are likely to mimic the market effects of another branded product, the FOB and pioneer manufacturer can avail themselves of the existing patent litigation procedures that apply to every industry, except generic small-molecule drugs. Biologic drug manufacturers have successfully used this process to resolve patent litigation for decades.²²² It is the same process all patent holders use to resolve claims of infringement or validity – the patent holder initiates infringement litigation after the FDA has approved the potentially infringing drug product, or the alleged infringer seeks a declaratory judgment of non-infringement or invalidity. For example, the Supreme Court has addressed biotechnology patent disputes in *Merck KGaA v. Integra Lifesciences I, Ltd.* and *MedImmune Inc. v. Genentech, Inc.*²²³ Lower courts also have addressed patent infringement litigation against competing products that had obtained FDA approval but had not yet been marketed.²²⁴

In other words, the patent holder can use existing court remedies to enforce its patent rights against an FOB, without developing special procedures that condition FDA approval on the outcome of patent litigation. Although the lack of a pre-approval patent resolution process increases the potential for at-risk launches by an FOB, a profit-maximizing FOB manufacturer is unlikely to enter the market "at-risk" if it believes it will

²²¹ See, e.g., David Reiffen and M.R. Ward, "Branded Generics" As A Strategy To Limit Cannibalization of Pharmaceutical Markets, 28 MANAGERIAL AND DECISION ECONOMICS 251, 264 (2005), available at http://fic.gov/be/healthcare/wp/12_Reiffen_BrandedGenericsAsAStrategy.pdf

²²² BIO Comment (9/30/08) at 22.

²²³ *MedImmune Inc. v. Genentech, Inc.* 549 U.S. 118, 137 (2007) (holding that a licensee has standing to bring a declaratory judgment action for non-infringement); *Merck KGaA v. Integra Lifesciences I, Ltd.*, 545 U.S. 193, 206-08 (2005) (clarifying 35 U.S.C.A. 271(e)(1)).

²²⁴ See, e.g., *Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1219 (Fed. Cir. 1991) (affirming trial court's finding that certain claims covering purified and isolated DNA sequences encoding EPO and host cells transformed or transfected with a DNA sequence were valid and infringed and reversing finding that other claims were enabled); *Amgen, Inc. v. Hoffmann-LaRoche Ltd.*, 2008 U.S. Dist. LEXIS 77343 (D. Mass. 2008) (granting permanent injunction for infringement of claims directed to a specific amino acid sequence); see also, *Amgen Inc. v. Hoechst Marion Roussel*, 579 F. Supp. 2d 199, 210 (D. Mass. 2008); *Bayer HealthCare LLC v. Abbott Labs.*, Civ. Action No. 6:08cv507 (E.D. Tex. Dec. 24, 2008). Abbott countersued in Massachusetts: *Abbott Labs. v. Bayer Healthcare LLC*, 09cv40002, U.S. District Court for the District of Massachusetts, 09cv40002 (D. Mass. June 5, 2009).

be liable for substantial infringement damages, cause physician and patient confusion, or harm its reputation as a reliable FOB drug manufacturer.

2. A Pre-Approval Patent Resolution Process is Unlikely to Provide Certainty and is Likely to Disrupt Innovation Incentives

A pre-approval patent resolution process is unlikely to achieve the certainty goals desired by pioneer and FOB manufacturers for three reasons. First, pioneer manufacturers with vulnerable patents have no incentive to have their patents invalidated or held not infringed by the FOB drug, especially if such a determination were to come several years before patent expiration or before FOB entry was imminent. In other situations, a pioneer manufacturer or third party may license its patents to other market participants where the license creates a revenue stream for the patent holder. If these patents are deemed invalid, the patent holder loses this revenue stream.

Experience under Hatch-Waxman shows that profit-maximizing manufacturers are likely to use a pre-approval regulatory process to delay a final court decision.²²⁵ In other instances, pioneer manufacturers may seek to bring suit in a judicial district with a history or reputation of slow-moving proceedings or they may fail to participate in the process, thus requiring the generic firm to bring a declaratory judgment action.²²⁶ Pioneer manufacturers also may attempt to hold back relevant patents during this pre-approval process if the regulations are subject to interpretation or the penalty for violating the rules provides an insufficient deterrent. These tactics can succeed because the FOB product has not been approved and the FOB manufacturer is unable to threaten market entry to further the process along.

By contrast, if litigation were to begin post-approval, the way in which branded biologic competitors resolve patent issues currently, a patent holder is likely to assert its strongest patents to keep the FOB product off the market. This process naturally focuses

²²⁵ Prior to 2003, if a branded manufacturer listed an additional patent in the Orange Book *after* the generic applicant filed its ANDA, more than one 30-month stay could be generated. The generic applicant was required to re-certify to this later-listed patent, and if, upon notice of the generic's re-certification, the brand-name company sued within 45 days, then FDA approval of the generic's previously filed ANDA was stayed for *an additional* 30-months from the notice date or until a court decision in the newly instituted patent litigation. FTC GENERIC DRUG STUDY at iii. In 2003, Congress amended the Hatch-Waxman Act to address this problem, "allowing lower-priced generic products to enter the market more quickly." Joint Explanatory Text to the MMA Conference Agreement, H.R. Conf. Rep. No. 108-391, at 836 (2003), *reprinted in* 2004 U.S.C.C.A.N. 2187. Now, a generic applicant who amends a pending ANDA to include Paragraph IV certifications to later-listed patents is not subject to a 30-month stay on the amended certification. 21 C.F.R. § 314.94(a)(12)(vi). This conduct is not unexpected. See Robert H. Bork, THE ANTITRUST PARADOX 347 (1978) ("The modern profusion of [...] governmental authorities offers almost limitless possibilities for abuse.").

²²⁶ See, e.g., *Teva Pharm., USA, Inc. v. FDA*, 182 F.3d 1003 (D. C. Cir 1999), *see also* Siwik at 289 ("[I]n Hatch-Waxman we learned that there are rules, but if there are no sticks, the rules are going to go out the window.").

litigation on the strongest patents, and reduces unnecessary pre-approval litigation regarding patents that may not be asserted after FDA approval.²²⁷

Moreover, without special pre-approval processes, there would be no need to change the declaratory judgment standards or rules. Even if the pioneer manufacturer did not initiate patent infringement litigation, the newly-approved FOB entrant would have standing to seek a declaration that the pioneer manufacturer's patents are invalid or not infringed.

Second, a start to litigation prior to FDA approval does not guarantee that patent issues will be resolved earlier than if litigation begins after FDA approval. Patents claiming the pioneer product may issue after a pre-approval process has begun, but before FOB approval. Patents also may issue after FOB approval. In either situation, the pioneer manufacturer, or third party, will need to bring additional litigation to enforce these later-issued patents, removing the certainty sought by the parties. The FOB's application and product also may change during the approval process, such that early patent litigation would no longer apply to the approved product. The litigation would be about a "moving target." Moreover, without an enforcement provision, even with a pre-approval process there is no guarantee that litigation will begin pre-approval. Until the FOB product is approved, patent infringement litigation may be premature.

Third, patent litigation under Hatch-Waxman shows that a pre-approval process is likely to invite numerous patent challenges. In the Hatch-Waxman context, nearly every branded drug faces a pre-approval patent challenge.²²⁸ Similarly, in the FOB context, a pre-approval patent resolution process may incentivize FOB manufacturers to challenge all of a pioneer product's patents in hope of exposing and exploiting weaknesses in the patent portfolio. In contrast, the absence of a pre-approval patent resolution process is likely to incentivize FOB manufacturers to direct their product development resources to those areas in which the pioneer product's patents are likely to be invalid or not infringed.

3. A Pre-Approval Process is Unlikely to be Workable and is Likely to Cause Harm

At a minimum, a pre-approval process must include two components: (1) notification requirements, including when notification begins; and (2) identification of patents to be litigated in the pre-approval period, which could include only "necessary" patents. The following sections describe how these procedures are unnecessary, could lead to anticompetitive outcomes, and defeat the purpose of a pre-approval process to obtain early resolution of potential patent infringement issues.

²²⁷ To the extent that the branded company brings suit in a slow-moving venue, the FOB has a variety of tools to force expeditious resolution of its case.

²²⁸ Norman at 201.

In addition, strong enforcement of the governing regulations for the pre-approval process will be necessary to deter abuse by the participants that seek to use the process to obtain competitive advantages. It is likely that a self-policing process will not work and that FDA will be asked to referee the process, much like it has been forced to do with the Hatch-Waxman process.

a. Notice Provisions are Unnecessary and Could Raise Anticompetitive Concerns

To be effective, a pre-approval patent resolution process will need to incorporate two major types of notice: (1) the pioneer manufacturer will need to provide notice to potential FOB manufacturers of patent claims covering its pioneer products; and (2) the FOB manufacturer will need to provide notice to the pioneer manufacturer of its FDA application.²²⁹

(1). Patents Claiming the Pioneer Drug Product are Publicly Available

Although the first type of notice is likely to help the FOB identify which patent claims its product may infringe, it is unnecessary given that granted patents and post-2000 patent applications are published by the PTO.²³⁰ FOB manufacturers can use existing databases to perform a patent search, as companies in many industries do, to determine patent claims that its product may infringe.²³¹ This search would apply to patents owned by the pioneer manufacturer and any applicable third parties.

In addition, the Patent Act currently requires patent holders to provide notice of potentially infringing patents. A patentee cannot recover damages for infringement until it (1) marks the product; or (2) provides the alleged infringer with actual notice of the infringement.²³² If the product, or its packaging, is not physically marked with applicable patent numbers, then the patentee can give notice either by sending a warning letter to the

²²⁹ Wyeth Comment (12/18/2008). Some panelists explained that there should be “[f]ull disclosure by all participants early in the patent resolution mechanism,” calling for patent holders to provide “full disclosure of the patents at issue in any dispute” while FOBs would provide “full disclosure of their application for regulatory approval, including all manufacturing process details.” *Id.*

²³⁰ Patent applications filed on or after November 29, 2000 are published eighteen months after the effective filing date of the application. One commenter noted the existence of “submarine” patent applications, a subset of patent applications filed before November 29, 2000 that are not published until the patent is granted. Applications with an effective filing date on or after June 8, 1995 expire 20 years from filing. Applications with an effective filing date before June 8, 1995 expire 17 years from patent grant. See Hospira Comment (9/22/08) at 4-5. While this can present issues of extended patent terms for old technology, this problem applies across the industry and likely does not outweigh the likely anticompetitive effects of a notice provision.

²³¹ See <http://www.uspto.gov/main/patents.htm>.

²³² 35 U.S.C.A. § 287(a) (2009).

alleged infringer, or by bringing a suit for infringement.²³³ The notice must identify the patent(s) and specifically allege infringement.²³⁴ For process patents only, an additional “request for disclosure” applies. Before it sells its product, a competitor or potential competitor may request a patent holder to produce all process patents that the patent holder believes could be infringed by the competitor’s product.²³⁵ These notice procedures would apply to follow-on biologic drugs even if there were no pre-approval patent resolution process.

A patent listing system also is likely to lead to anticompetitive unintended consequences. For example, Hatch-Waxman’s notice provision led to the delay of generic entry until the notice provisions were amended by the Act’s 2003 Amendments. As discussed above, a branded manufacturer must list certain patents in the FDA’s Orange Book.²³⁶ The generic then files a certification regarding each patent. If the branded manufacturer then brings an infringement action within 45 days, FDA approval of the ANDA automatically is stayed for 30 months.²³⁷

Over time, branded manufacturers began successively to list later-issued patents in the Orange Book. A number of these later-listed patents did not meet the FDA’s requirements for listing patents in the Orange Book and were subsequently found to be invalid or not infringed.²³⁸ This strategy allowed the branded manufacturer to obtain additional 30-month stays delaying FDA approval of generic drugs. Congress remedied this problem in the Medicare Modernization Act by limiting branded drug companies to a single 30-month stay, but only after consumers lost substantial competition from generic drugs during the periods of these “stacked” 30-month stays.

(2). Notice of the FOB’s Application Raises Competitive Concerns

The FOB manufacturer’s notice to the pioneer manufacturer of its FDA application and additional manufacturing information raises two concerns – one administrative and one anticompetitive. First, there is a difficulty in determining to whom the notice should be provided. Biologic drug patents implicate more than the pioneer manufacturer; they also

²³³ *American Medical Sys., Inc. v. Medical Eng’g Corp.*, 6 F.3d 1523, 1538 (Fed. Cir. 1993).

²³⁴ *Amstead Indus., Inc. v. Buckeye Steel Castings Co.*, 24 F.3d 178, 185-87 (Fed. Cir. 1994) (finding lack of notice where the letter did not specifically charge the recipient with infringement and did not identify an infringing device).

²³⁵ 35 U.S.C.A. § 287(b)(4) (2009).

²³⁶ See 21 U.S.C.A. § 355(b)(1) (2009) and Appendix B for a detailed description of the Hatch-Waxman abbreviated drug approval process.

²³⁷ 21 U.S.C.A. § 355(j)(2)(A)(vii)(IV) and § 355(j)(5)(B)(iii) (2009).

²³⁸ Fed. Trade Comm’n, *GENERIC DRUG ENTRY PRIOR TO PATENT EXPIRATION: AN FTC STUDY 18* (July 2002), available at <http://www.ftc.gov/os/2002/07/genericdrugstudy.pdf>.

implicate universities and third parties. If notice is provided only to the pioneer manufacturer, an early start to patent resolution may not involve all of the relevant parties and patents, thus defeating the purpose of the pre-approval process. Conversely, if notice is provided to all parties, it may overly complicate the process and deter early resolution. Indeed, one panelist suggested “[t]he whole issue of notice should be as simple as possible, but some of the issues are more complex than we see even in the more complex drug situations.”²³⁹ This complexity is likely to reduce the effectiveness of a notice requirement and raise questions over whether sufficient notice had been provided in a timely manner.

In addition, requiring the FOB manufacturer to provide a detailed description of the product and manufacturing processes to the pioneer manufacturer and other third parties could facilitate anticompetitive conduct.²⁴⁰ As discussed in Chapter 1, the FOB manufacturer is likely to compete against the pioneer product with a similar, but not identical, product. The FOB product could be an improvement over the pioneer product in terms of reduced dosing, increased effectiveness, or fewer side effects. In other cases, the FOB product manufacturer may have discovered a way to manufacture an FOB product more efficiently than the pioneer manufacturer. In either scenario, the firms are likely to be significant rivals and engage in head-to-head competition.

Forced sharing of information between rivals about the timing and content of the FOB’s application and manufacturing processes (and other related matters) could facilitate collusion.²⁴¹ For example, this information could facilitate agreements to delay entry, allocate markets, or fix prices. Experience under Hatch-Waxman has shown that generic and branded competitors have entered into “pay-for-delay” patent settlements that delay entry. In other situations, the anticompetitive harm could stem from providing the pioneer manufacturer with competitively sensitive information that it otherwise would not be able to obtain. The pioneer manufacturer may then have an opportunity to act on this information prior to the approval of the FOB and thus, can pre-empt the innovation and price competition that is likely to occur with FOB entry. This harm is lessened, although not eliminated, with patent litigation after FDA approval because the FOB can enter quickly and blunt any harm that could be caused by a sharing of competitively significant information.

Moreover, sharing this type of information may be unnecessary to the extent that the FOB manufacturer claims that the pioneer manufacturer’s patents are invalid. In these

²³⁹ Seide at 266.

²⁴⁰ Kushan at 257-58 (“[T]he notice should include a detailed description of the FOB’s product, including the amino acid sequence produced, the nucleic acid sequence, expression technologies, process technologies, manufacturing process information, molecular structure, formulation, patent certifications, molecular identity and intended uses.”).

²⁴¹ Fed. Trade Comm’n and U.S. Dep’t of Justice, ANTITRUST GUIDELINES FOR COLLABORATIONS AMONG COMPETITORS 12 (2000).

situations, the pioneer manufacturer has no need for detailed information relating to the FOB's method of manufacturing.²⁴²

Confidentiality provisions that limit access to information about the FOB product to persons involved in the pre-approval patent litigation process are likely to be ineffective to safeguard against these potential anticompetitive harms. Biotechnology patent litigation is a complex endeavor that requires not only patent attorneys, but medical, scientific, manufacturing, and business personnel with intimate knowledge about the pioneer product's patent claims. There is no way to cordon off a patent infringement analysis regarding the FOB drug product from the personnel that know the most about the pioneer product.²⁴³

b. Identification of a Subset of Patents to Resolve During the Pre-Approval Patent Resolution Process Defeats the Purpose of a Pre-Approval Resolution Process

A pre-approval patent resolution process will need to account for the broad range of patents claiming a pioneer product and their multiple owners. As described in Chapter 2, the types of patents that are likely to claim the biologic product include compound or molecule patents, method of treatment, formulation and dosage form patents, and manufacturing process and technology platform patents. Due to the nature of biologic drugs, these portfolios may include patents owned by the pioneer manufacturer,²⁴⁴ as well as third-party owned patents that are licensed either exclusively or non-exclusively to the pioneer manufacturer.

Panelists representing pioneer manufacturers proposed that a pre-approval patent resolution process resolve all of the patents claiming a pioneer product.²⁴⁵ Another panelist noted that the process should include third-party patents, reasoning that if the patent resolution process does not cover third-party patents, then the generic will be susceptible to launch-at-risk on those patents.²⁴⁶

²⁴² Patent law places the burden of proof of demonstrating infringement on the patent holder. The patent holder may not need the FOB's application to establish infringement if the FOB's product already is approved. In addition, a notice provision is likely to have the effect of shifting the burden of proof such that the FOB has to demonstrate that it does not infringe the patent, rather than under patent law having the patent holder show that its patent has been infringed.

²⁴³ Of course, these arguments apply with equal force in the opposite scenario if the FOB manufacturer were to obtain confidential information regarding the branded product.

²⁴⁴ The pioneer manufacturer-owned patents may be out-licensed further to additional third parties.

²⁴⁵ Kushan at 237.

²⁴⁶ Seide at 238 ("The technology platform patents are very important . . . and so there has to be some way of resolving third-party patents as well if they're known.").

As a counterpoint, panelists said that litigating all patents potentially infringed by the FOB product could lead to delay. If the process is not tailored, litigation costs could outweigh benefits for some FOB companies.²⁴⁷ Commenters representing FOB manufacturers explained that the process should be limited to “necessary” patents (*i.e.*, patents that would most likely prevent the FOB from entering the market). One commenter explained that “it is in the generic’s interest to immediately litigate only those patents that would prevent the generic company from launching until questions of validity, enforceability, or infringement are resolved. Litigation on all remaining patents would take place after the generic product actually enters the market.”²⁴⁸

It is unclear how a regulatory process could determine which patents are “necessary.” Resolving infringement issues for a subset of “necessary” patents may streamline that particular litigation, but it is likely to lead to future uncertainty. A patent not deemed “necessary” does not mean that the patent is invalid and/or not infringed by the FOB manufacturer. The patent holder can still assert these “unnecessary” patents following FDA approval of the FOB. Retaining these later “unnecessary” patents is unlikely to create the certainty that a pre-approval patent resolution process is intended to create. As noted above, additional patents that block FOB entry may issue after the pre-approval process has started, thus complicating identification of “necessary” patents and frustrating the overall objective of the pre-approval process to obtain certainty regarding patent infringement issues.

Furthermore, a two-tier resolution system whereby some patents are “necessary” and litigated pre-approval, while others must wait until after FDA approval, will likely create additional litigation regarding the determination of “necessary” versus “unnecessary” patents. Such litigation will create additional costs detrimental to consumer welfare. Moreover, as discussed above, Hatch-Waxman created the incentive for the branded manufacturer to “stack” patent notification to obtain multiple 30-month stays. Here, too, limiting the process to a subset of patents may create incentives for the brand to withhold certain “necessary” patents to retain their rights after FDA approval of the FOB product.

c. Enforcement Provisions May Harm Innovation and Competition

An enforcement provision is likely to be necessary to ensure that the notice and patent identification requirements are adhered to during the pre-approval resolution process. Without such an enforcement mechanism, the pre-approval process is unlikely to be adhered to, and likely to cause unintended consequences that delay FOB entry.

²⁴⁷ Siwik at 226.

²⁴⁸ Barr Comment (9/30/2008) at 10; CCPM Comment (9/30/2008) at 8; GPHA Comment (9/30/08) at 6; Teva Comment (9/30/08) at 6; Leicher at 260 (“If you limit it to the key patents that are built around the product that the brand company controls, I think you’ve got it simplified.”).

Several panelists and commenters suggested that a “sue-or-lose” provision in which a pioneer manufacturer, or third party, could lose its patent enforcement rights if it did not participate in the patent resolution process, is necessary to ensure the integrity of the pre-approval patent resolution process.²⁴⁹ One panelist said that without a penalty provision, the rules likely will not be enforced, noting that if the pioneer manufacturer holds back patents until the end of the exclusivity period, or launch, then any likely effect of early resolution will not be achieved.²⁵⁰

Panelists representing pioneer manufacturers opposed a sue-or-lose provision or a provision in which damages are limited for lack of participation in the process.²⁵¹ One commenter said that it likely would lead to gaming, “the patent owner would be forced to decide whether to sue based on the information it obtained from the FOB applicant. That applicant, in turn, would have an incentive to convince the patent owner not to bring a suit.”²⁵² Another panelist explained that a sue-or-lose provision would take away a valuable property right from the patent holder for failure to comply with a regulatory obligation.²⁵³

²⁴⁹ Schultz at 290; Essential Action Comment (12/20/2008) at 6 (“[I]nitial registrants should be required at the time of the application to indicate any granted or filed patents that they believe apply to the biologic for which they seek marketing approval. This should include both patents granted to the registrant or which have been licensed to them. They should be required to update this list for any new patent filings, within a statutorily defined period, perhaps 30 days. Failure to disclose should forfeit the right to enforce.”).

²⁵⁰ Siwik at 289 (“If the overall scheme is fair and balanced, maybe we don’t need to worry about huge sticks to make people participate, but in Hatch-Waxman we learned that there are rules, but if there are no sticks, the rules are going to go out the window. There were statutory definitions of what patents could go in the Orange Book, and there were a few companies that abused that, and a list of other patents triggered a lot of 30 month stays, and a lot of litigation delays, but no penalties for doing it.”).

²⁵¹ Goldman at 287; Kushan at 293 (current laws exists to manage parties who timely fail to enforce their patent rights); PhRMA Comment (12/22/08) at 5.

²⁵² PhRMA Comment (12/22/08) at 5 (The proposal also “could create artificial incentives to litigate, which would waste time and money and impose burdens that would not be beneficial for the patent or the judicial system.”).

²⁵³ Seide at 288.

Based on experience with the patent resolution process in Hatch-Waxman, examples of the need for enforcement could include:

- If the patent holder's notice fails to include all of the patents or all of the "necessary" patents claiming the pioneer product;
- If the patent holder fails to update the notice to include patents issued after the patent litigation has begun;
- If the FOB applicant fails to provide a sufficiently detailed description of the FOB product, its method of manufacture, or the materials included in the manufacturing; or
- If either the pioneer manufacturer or FOB applicant fails to provide information in a timely manner.

Experience under Hatch-Waxman also demonstrates that the FDA will be pulled into these disputes and asked to resolve substantive patent issues to enforce the rules in any patent resolution process.²⁵⁴ Under Hatch-Waxman, the FDA has been asked to determine whether patents are correctly listed in the Orange Book. The FDA has consistently maintained that it does not have the patent expertise to do so.²⁵⁵ Its resources are likely to be best deployed in examining the safety and effectiveness of FOBs, not in policing a patent resolution process for which it has little experience and expertise.

If the FDA were not involved, an enforcement provision could be designed so that if a party did not sue under the patent resolution process in a timely manner, it would lose its rights to later enforce the patent under provision of the Patent Act. This provision is beneficial because in order for the process to have integrity, there must be a mechanism to compel parties to participate. On the other hand, it is likely to be an unduly harsh remedy in the face of uncertainty as to a determination of "necessary" patents to include in a notice or the extent of detail in the FOB applicant's notice describing its product and its method of manufacturing. Such a remedy may also unnecessarily affect the patent holder's right to

²⁵⁴ See, e.g., *Sandoz, Inc. v. F.D.A.*, 439 F. Supp. 2d 26 (D.C. Cir. 2006) (denying generic competitor's motion for injunctive relief against FDA re-listing brand patents); *Purepac Pharm. Co. v. TorPharm, Inc.*, 354 F.3d 877, 886-88 (D.C. Cir. 2004) (upholding FDA decision to delist a patent incorrectly listed for the wrong drug); *Dr. Reddy's Labs., Inc. v. Thompson*, 302 F. Supp. 2d 340, 355 (D.N.J. 2003) (upholding FDA delisting of an expired patent and not to award exclusivity to an ANDA applicant who filed a paragraph IV certification before the patent's expiration);

²⁵⁵ See, e.g., *American Bioscience, Inc. v. Thompson*, 269 F.3d 1077, 1080 (D.C. Cir. 2001) (recognizing that the FDA "has refused to become involved in patent listing disputes, accepting at face value the accuracy of NDA holders' patent declarations and following their listing instructions"); *Purepac Pharm. Co. v. Thompson*, 238 F. Supp. 2d 191, 196 (D. D.C. 2002) ("The duty to ensure that the Orange Book only lists patents that actually claim approved drugs . . . lies with NDA holders.") (citing *Watson Pharm., Inc. v. Henney*, 194 F. Supp. 2d 442, 445-46 (D. Md. 2001) ("In making its decision to list a patent . . . it is entirely appropriate and reasonable for the FDA to rely on the patentee's declaration as to coverage, and to let the patent infringement issues play out in other, proper arenas, as is the clear intent of the Hatch-Waxman Amendments.")).

assert the patent in unrelated contexts. Resolving these uncertainties (and others) is likely to delay resolution of patent issues and, thus, defeat the purpose of a pre-approval patent resolution process.²⁵⁶

In sum, although there may be legitimate issues about invalid or not infringed patents blocking FOB drug entry, these issues are best handled post-FDA approval when the parties' incentives are not distorted by a pre-approval process. In other words, post-FDA approval, the FOB manufacturer will seek to begin commercial marketing and the pioneer manufacturer will seek to obtain a preliminary injunction to block FOB drug entry.

²⁵⁶ For example, if the rules required a pioneer manufacturer to provide a list of patents within 30 days, but one patent is left off and corrected on day 31, does this omission limit enforceability against that FOB manufacturer? There are countless ways in which parties may inadvertently violate the rules for which a "sue-or-lose" provision would extinguish their patent rights.

CHAPTER 4 **LIKELY COMPETITIVE EFFECTS OF A MARKET EXCLUSIVITY PERIOD FOR FOLLOW-ON BIOLOGICS**

The Hatch-Waxman Act provides a 180-day marketing exclusivity period to the first generic drug applicant that seeks FDA approval prior to the expiration of patents relating to the branded drug product.²⁵⁷ No other generic manufacturer may obtain FDA approval to market its product until the first generic has sold its product for 180 days or has forfeited the exclusivity period.

The 180-day exclusivity period incentivizes generic manufacturers to challenge the patents claiming a branded drug product. One court has explained that the 180-day exclusivity rewards the first generic applicant for the expense and effort involved with patent challenges.²⁵⁸ A court finding of patent invalidity benefits not only the challenger, but also subsequent generic applicants whose entry is no longer blocked by the patent. Thus, the 180-day marketing exclusivity period prevents immediate free-riding by subsequent generic applicants on a favorable outcome that results from the first applicant's patent challenge. As subsequent generic firms enter, generic prices can drop to 80 percent off the branded price, depending upon the number of entrants.²⁵⁹ The exclusivity period permits the first generic entrant to recoup its patent litigation costs before the substantial price drop caused by multiple generic entrants.

This chapter summarizes the commenters and panelists views on the need for, and the likely effects of, providing FOB manufacturers with incentives to develop their products by restricting entry of competing products during an FOB exclusivity period. It then explains that an exclusivity period is unnecessary to encourage the development and marketing of biosimilar products. Biosimilar products are likely to earn substantial profits without regulatory exclusivity periods. Moreover, European and U.S. experience with biosimilars shows that sufficient profit incentives already exist to encourage biosimilar entry.

An exclusivity period is likely to be unnecessary to encourage the development of interchangeable biosimilar drug products because potential market opportunities appear robust. The competitive dynamics that justified the 180-day exclusivity period for small-molecule generic drugs are unlikely to be present with the entry of interchangeable biosimilar drugs.

It also is unclear that an exclusivity period will successfully incentivize a manufacturer of a biosimilar product to develop an interchangeable FOB product. Biosimilar manufacturers are likely to make this additional investment based on a

²⁵⁷ 21 U.S.C.A. § 355 (j)(5)(B)(iv)(I) (2009).

²⁵⁸ *Mova v. Shalala*, 140 F.3d 1060, 1074 (D.C. Cir. 1998).

²⁵⁹ See David Reiffen & Michael Ward, "Branded Generics" As A Strategy To Limit Cannibalization of Pharmaceutical Markets, 28 *MANAGERIAL AND DECISION ECONOMICS*, 251, 264 (2005), available at http://frc.gov/be/healthcare/wp/12_Reiffen_BrandedGenericsAsAStrategy.pdf.

consideration of, among other things: the cost, expected prices, capacity constraints, and the extent and effect of state substitution laws. This situation contrasts significantly with small-molecule generic competition seen under Hatch-Waxman in which generic manufacturers enter initially with an interchangeable product. Unlike FOB manufacturers, generic manufacturers do not market a “similar” product first and replace it with an “interchangeable” product later.

Not only do market dynamics counsel against an FOB exclusivity period, but the anticompetitive delay in entry evidenced in small-molecule generic drug markets is likely to be repeated if an exclusivity provision for interchangeable FOBs is implemented.²⁶⁰ The current 180-day exclusivity period exacerbates the problem of “pay-for-delay” settlements that prevent generic entry.²⁶¹

Awarding an FOB exclusivity period on a “first-to-approve” rather than a “first-to-file” basis does not lessen the potential harm. These anticompetitive consequences are likely to result if the period can be extended, the period does not run immediately upon its award, or if a firm has the ability to delay triggering the running of the period through, for example, a patent settlement, acquisition, merger, or agreement.²⁶²

I. NECESSITY OF AN EXCLUSIVITY PERIOD TO ENCOURAGE DEVELOPMENT OF FOLLOW-ON BIOLOGIC DRUGS

The question arises whether an FOB manufacturer needs an incentive beyond market-based pricing to develop an interchangeable FOB drug, such as a limit on when subsequent interchangeable FOB drug entry can occur (an “FOB exclusivity period”). This limitation would allow the first interchangeable FOB manufacturer to recoup its development expenses.²⁶³ One commenter indicated that “most companies contemplating biogenerics will be reluctant to invest the significant resources required to

²⁶⁰ See FDA/Center for Drug Evaluation and Research, *180-Day Generic Drug Exclusivity* (2001), available at http://www.fda.gov/cder/about/smallbiz/generic_exclusivity.htm#COURT (“This 180-day exclusivity provision has been the subject of considerable litigation and administrative review in recent years...”).

²⁶¹ See *How Pay-for-Delay Settlements Make Consumers and the Federal Government Pay More for Much Needed Drugs: Hearing Before the Subcomm. on Commerce, Trade, and Consumer Protection of the H. Comm. on Energy and Commerce*, 111th Cong. (2009) (Prepared Statement of the Federal Trade Commission), available at <http://www.ftc.gov/os/2009/03/P859910payfordelay.pdf>.

²⁶² For an example of how exclusivity periods can be extended, see discussion *supra* in Chapter 3 regarding stacking of 30-month stay provisions under Hatch-Waxman.

²⁶³ See, e.g., Momena Comment (12/22/08) at 7 (“The discovery and understanding of the biology of a pathway often allows for patent protection that not only covers the therapeutic protein or antibody itself, but offers the potential to claim coverage of other therapeutic proteins and antibodies that regulate the biological landscape in which the biologic acts.”); *id.* at 7; Pearce at 169; Hospira (Wilkie Farr) Comment (12/22/08) at 2; Leicher at 161-62.

determine interchangeability if there is no possibility for recouping the costs that come with patent challenges.”²⁶⁴

By contrast, other commenters and panelists suggested that there was no need for an FOB exclusivity period because potential market profits would provide sufficient incentives to enter with a follow-on product.²⁶⁵ Another commenter explained that if the market did not provide sufficient incentives on its own, an FOB exclusivity period would not do so either. An applicant would already have the assurance of *de facto* exclusivity, because there would not likely be a second or subsequent entrant, and *de jure* exclusivity would add nothing to the economic calculus.²⁶⁶

One potential FOB entrant explained that if a company invests a huge amount of money developing FOB products, it is unwise to put up further barriers in the form of exclusivity granted to other FOBs against its ability to get a return on investment.²⁶⁷ Others panelists stressed that an additional incentive to foster FOB entry is no longer needed because the environment in 2008 is much different than it was in 1984, when Hatch-Waxman was enacted and there were no established generic competitors, thus an incentive was necessary to jump start the industry.²⁶⁸

Other panelists questioned why an FOB exclusivity period was needed in the United States, the largest drug market in the world, when follow-on drug manufacturers in Europe have not needed exclusivity to incentivize biosimilar entry. One panelist noted that European regulatory structure does not provide market exclusivity for biosimilars or

²⁶⁴ Teva Comment (9/30/08) at 6; *see also* Barr Comment (9/30/08) at 8 (“market exclusivity is necessary to encourage companies to develop generic biologics” and that “generic companies need an incentive to undertake costly and time-consuming patent disputes – disputes needed for pre-patent expiration generic market entry.”); GPhA (9/30/08) at 5 (generic marketing exclusivity provides “the incentive needed for generic companies to undertake the considerable risk that comes with navigating intellectual property for the brand product and patent. Biogeneric companies will be very reluctant to invest resources if there is no possibly for recouping the costs that come with patent challenges.”); Winston & Strawn (Hospira) Comment (12/22/08) at 2.

²⁶⁵ Norman at 197 (“to recognize why someone following on after the trail has already been blazed should need any incentive other than the market in and of itself. The market provides plenty incentives for people to do what reasonable persons do every day”); Zielinski at 196 (The “market dynamic itself will be sufficient incentive, because fewer entrants, and less price discount, so FOBs can make it up in sales.”); *see also* *Competition in the Pharmaceutical Marketplace: Antitrust Implications of Patent Settlements: Hearing Before the S. Comm. On the Judiciary*, 107th Cong. (2001) (statement of Orin Hatch, Chairman, (S. Comm. On the Judiciary) (“Is it necessary or advisable to retain the 180-day exclusivity period given the enormous financial incentives to challenge patents on blockbuster drugs?”).

²⁶⁶ Eli Lilly Comment (12/22/08) at 5.

²⁶⁷ Allan at 194, 207.

²⁶⁸ Miller at 198-99; *see also* Amgen Comment (9/30/08) at 19 (“[T]he generic industry is in a very different place today than it was at the time the Hatch-Waxman pathway for approval of generic drugs was adopted. In 1984, the industry was not yet established and success of the generic business model was uncertain.”).

“for any generic of any kind, including small molecule.”²⁶⁹ This panelist also concluded that because many generic companies do not make the 180-day period the cornerstone of their business model, the 180-day marketing exclusivity period is not necessary to encourage entry.²⁷⁰ A commenter also noted that the large number of biosimilar products under development in Europe, where no market exclusivity is provided for biosimilar products, indicates that market exclusivity in the United States may be unnecessary.²⁷¹

II. MARKETING EXCLUSIVITY LIMITED TO INTERCHANGEABLE FOLLOW-ON BIOLOGICS

Panelists suggested that any regulatory exclusivity period be limited to interchangeable FOBs (*e.g.*, biogenerics), which may cost more to develop than biosimilar drug products.²⁷² One panelist indicated that demonstrating interchangeability may require clinical trials. The trials will be complicated and expensive if there are multiple interchangeable products.²⁷³ A commenter suggested that a “short period of exclusivity for the first to market could provide an incentive to companies entering the biogeneric market; however, companies will not likely rely on winning exclusivity to invest in the products because the development time and investment for biogenerics is so great.”²⁷⁴

Some panelists suggested that there are likely to be few, if any, interchangeable FOB entrants because of the additional expenses to develop and obtain approval of interchangeable products.²⁷⁵ In contrast, another panelist predicted that the *availability* of an FDA approval process for interchangeability would prompt the development of the necessary analytics needed to prove interchangeability.²⁷⁶

If there were an FOB exclusivity period, panelists described how experience under Hatch-Waxman provided insights into how best to structure the exclusivity to

²⁶⁹ Barkoff at 204-05; *see also* Zielinski at 206; Teva Comment at 5 (“Exclusivity periods should be based on the entirety of a particular regulatory and patent system. The exclusivity periods provided in the EU are not a legitimate model for guiding the U.S. since, for example, price controls are prevalent in the EU, while the U.S. does not impose price controls.”).

²⁷⁰ Barkoff at 205-06.

²⁷¹ *See* Amgen Comment (9/30/08) at 19.

²⁷² Hospira Comment (12/22/08) at 7 (“[t]he R&D investment for a biogeneric is significantly greater and could approach \$100 million”); *see also* Berhman Presentation at 13; Momenta Comment (9/30/08) at 3; Schultz at 191-92.

²⁷³ Allan at 194.

²⁷⁴ Hospira Comment (12/22/08) at 7.

²⁷⁵ Shultz at 194-95.

²⁷⁶ Brugger at 74.

avoid unintended anticompetitive effects that delayed entry. One panelist suggested that an FOB exclusivity period should restrict only other interchangeable FOBs, not other biosimilars, from coming to market during that period of time.²⁷⁷

One commenter posited that the Hatch-Waxman 180-day marketing period was designed to incentivize generic drug applicants to engage in patent litigation because of the concern that other generic drug applicants would free-ride on this litigation investment.²⁷⁸ One panelist suggested that placing a bounty system on intellectual property rights through the awarding of marketing exclusivity for patent challenge is not in the public interest.²⁷⁹ Other commenters suggested that FOB exclusivity “be based on product approval rather than patent challenge” such that it does not create a “perverse incentive to challenge the innovator’s patent early and often, regardless of the merit of the challenge.”²⁸⁰

III. ANALYSIS OF LIKELY COMPETITIVE EFFECTS OF AN FOB EXCLUSIVITY PERIOD

An FOB exclusivity period is unnecessary to encourage the development and marketing of biosimilar products. Market forces to incentivize the development of these products appear robust. Indeed, several panelists and commenters noted that the multi-billion dollar size of the market opportunities, the European experience of HGH and EPO biosimilar entrants, and the U.S. EPO biosimilars provide strong evidence to predict that regulatory incentives are unnecessary to encourage biosimilar products in the United States.²⁸¹ Moreover, they are likely to face less competition than small-molecule generic drug manufacturers because of the high entry costs.

²⁷⁷ Shultz at 201-02; *see also* Barr Comment (9/30/08) at 8 (if there were an exclusivity period that it “not prevent the immediate approval of a non-interchangeable, but comparable, generic biologic product” and that it be awarded “to the first interchangeable product to be approved by FDA, rather than to the company that filed the first application seeking approval of such a product, as happens under Hatch-Waxman”); Mylan Comment at 9 (exclusivity provided only to the first biogeneric would not prevent or delay the FDA’s approval of a biosimilar product); Novartis Comment (12/22/08) at 18 (“[t]o date, none of the U.S. legislative proposals for FOBs would grant exclusivity to a non-interchangeable FOB. An interchangeability designation is currently considered the most effective way to introduce head-to-head market-based competition with currently-licensed PHS Act biologics.”); Teva Comment (10/8/08) at 8.

²⁷⁸ BIO Comment (9/30/08) at 24-25 (“patent litigation over one FOB product will not necessarily apply to another FOB product,” and the risk of litigation free-riders faced in the generic small-molecule context will be much diminished in an FOB context); *see also* PhRMA Comment (9/30/08) at 21 (“[it] is not clear that regulatory exclusivity would be need to encourage patent challenges under an FOB regulatory pathway.”).

²⁷⁹ Norman at 201.

²⁸⁰ Amgen Comment (9/30/08) at 24 (expressing concern that “excessive patent litigation spawned by the 180-day exclusivity provision” would increase the cost of producing new treatments and cures); *see also* Shultz at 192.

²⁸¹ *See* Grabowski at 39; Heldman at 22-32; Heldman Presentation at 3-9; Lane at 36-37, 40; Urlep at 34; Zielinski at 211; Amgen Comment (9/30/08) at 19 (“It appears from the number of biosimilar products under development in Europe, where no market exclusivity is provided for biosimilar products, that market

An FOB exclusivity period also is unlikely to be necessary to encourage the development of interchangeable biosimilar drug products for several reasons. First, the conditions that justified the 180-day exclusivity period for small-molecule generic drugs under Hatch-Waxman are unlikely to be present. Interchangeable FOB drug prices are unlikely to fall as much (either in real terms or as a percentage of the pioneer product's price) as they do when multiple small-molecule generic drugs enter the market. In the small-molecule generic drug context, the first generic entrant is able to recoup its patent litigation costs before entry of additional generic drugs. Additional generic entry substantially decreases the generic price, in some cases, up to 80 percent off the referenced product's price. It is likely, however, that few interchangeable FOB entrants will enter the market, and prices will not fall as much as they do following small-molecule generic drug entry.

Second, it is unclear whether subsequent interchangeable entrants would be able to "free-ride" on the first interchangeable's FDA approval or patent litigation expense and thus enter the market once the first interchangeable product is approved. It is expected that FDA approval of interchangeable products (and accompanying patent litigation) is likely to be more complicated than generic drug approval. Unlike generic small-molecule drugs where several generic drug products often await FDA approval once a patent expires or is found invalid or not infringed, this complexity is likely to diminish the prospect that a "queue" of interchangeables will be ready for approval once the first interchangeable product is approved. Thus, the circumstances that justified a 180-day marketing exclusivity period for generic drugs are unlikely to be present for interchangeable FOB drug products.

Third, it is uncertain that cost will justify an FOB exclusivity period. It may not cost substantially more to show that a biosimilar product is interchangeable with the referenced branded product than an initial finding of biosimilarity. If technology advances such that it is relatively inexpensive to determine interchangeability, an exclusivity period is unnecessary.

Fourth, it is unclear that an FOB exclusivity period will successfully incentivize a manufacturer of a biosimilar product to develop an interchangeable FOB product. Biosimilar manufacturers are likely to make this additional investment based on a consideration of, among other things, the cost, expected prices, capacity constraints, and the extent and effect of state substitution laws. This situation contrasts significantly with small-molecule generic competition seen under Hatch-Waxman in which generic manufacturers enter initially with an interchangeable product. Unlike FOB manufacturers, generic manufacturers do not market a "similar" product first and replace it with an "interchangeable" product later.

Not only is an FOB exclusivity period not justified by market conditions but the delay in generic entry evidenced in small-molecule generic drug markets is likely to be

exclusivity for biosimilars in the United States may not be necessary."); Bernstein Research Comment at 12.

repeated in biologics markets if an exclusivity provision for interchangeable products is implemented. These anticompetitive consequences are likely to result if the period can be extended, the period does not run immediately upon its award, or if a firm has the ability to delay triggering the running of the period through, for example, a patent settlement, acquisition, merger, or agreement.²⁸² In addition, each of these problems is likely to be present even if the exclusivity is awarded on a “first-to-file” rather than a “first-to-apply” basis.

For example, pioneer manufacturers and FOB applicants could settle patent litigation such that a payment is made to the first interchangeable FOB entrant to settle the patent dispute and defer its entry. This settlement could create a bottleneck that blocks subsequent interchangeable FOB from obtaining FDA approval because the first-approved product’s exclusivity period has not run. This outcome results in significant harm to consumers who not only lose the benefit of the first interchangeable product’s entry but also the second product’s entry. Furthermore, in this circumstance, the rationale for the FOB exclusivity period is undermined by proof that the subsequent applicant did not need an additional incentive to perform all the steps necessary to enter the market, yet is blocked from the market by the first interchangeable product.

In theory, various regulatory fixes could require an interchangeable FOB manufacturer to forfeit its exclusivity period. These forfeiture events could include when: (a) it fails to trigger the running of the period by launching the interchangeable FOB product immediately following a final court decision in its favor on the patents at issue; (b) it has not been sued by the branded manufacturer, or (c) its patent suit is taking too long to resolve and a subsequent interchangeable applicant is approvable by the FDA.

The problem with these fixes is that each one blocks entry of a subsequent interchangeable product for a period of time and thereby denies consumers price competition and increased innovation. They also require the FDA to expend significant resources monitoring patent registrations and certifications, litigations, and marketplace activity that is outside its core missions and competencies.²⁸³ Further, such a marketing exclusivity provision will inevitably generate lawsuits against the FDA regarding award,

²⁸² For an example of how exclusivity periods can be extended, see discussion in Chapter 3 regarding stacking of 30-month stay provisions under Hatch-Waxman.

²⁸³ 21 U.S.C.A. § 355(b)(1); see, e.g., *Teva Pharm. USA, Inc. v. Leavitt*, 548 F.3d 103, 106-07 (D.C. Cir. 2008); *Ranbaxy Labs. Ltd. v. Leavitt*, 469 F.3d 120, 124 (D.C. Cir. 2006); *Sandoz, Inc. v. F.D.A.*, 439 F. Supp. 2d 26, 30 (D.C. Cir. 2006); *Apotex, Inc. v. Thompson*, 347 F.3d 1335, 1348-49 (Fed. Cir. 2003); *Pharma Inc. v. Thompson*, 296 F.3d 227, 242-43 (4th Cir. 2002); *Andrx Pharm., Inc. v. Biovail Corp.*, 276 F.3d 1368, 1373-74 (Fed. Cir. 2002); *Mylan Pharm., Inc. v. Thompson*, 268 F.3d 1323, 1331-32 (Fed. Cir. 2001); *Am. Bioscience, Inc. v. Thompson*, 269 F.3d 1077, 1080 (D.C. Cir. 2001) (recognizing that the FDA “has refused to become involved in patent listing disputes, accepting at face value the accuracy of NDA holders’ patent declarations and following their listing instructions”); see also *Prepared Statement of the Federal Trade Commission Before the Hearing before the S. Comm. on Commerce, Science, and Transportation*, 107th Cong. (2002) (statement of Timothy J. Muris, Chairman, FTC), available at <http://www.ftc.gov/os/2002/04/pharmtestimony.htm>.

timing, scope and termination of the marketing exclusivity periods as has occurred regarding the 180-day provision of the Hatch-Waxman Amendments.²⁸⁴

For these reasons, an FOB exclusivity period is unlikely to benefit consumers either with an increase in the pace or scope of innovation or additional price competition. An FOB exclusivity period is likely to delay FOB competition in the case when a second interchangeable FOB applicant is ready to be approved, but cannot enter until the first-approved interchangeable product's exclusivity has expired.

²⁸⁴ See, e.g., *Mova Pharm. Corp. v. Shalala*, 140 F.3d 1060, 1065 (D.C. Cir. 1998); *Apotex, Inc. v. FDA*, No. 06-5105, 2006 U.S. App. LEXIS 10561 (D.C. Cir. Apr. 24, 2006), *aff'd* *Apotex, Inc. v. FDA*, No. 06-5105, 2006 U.S. App. Lexis 14086 (D.C. Cir. June 6, 2006) ("This case is the latest flare-up in a long running dispute between the Food and Drug Administration (FDA) and several generic manufacturers as to what qualifies under the Hatch-Waxman act as "a decision of a court . . . holding [a challenged] patent to be invalid or not infringed.").

APPENDIX A

Economists have developed a framework to calculate the time it takes for a branded biologic drug manufacturer to recover fully its investment to develop and commercialize a typical biologic drug. This framework is referred to as the “Nature model” because it first appeared in an article by Dr. Henry Grabowski in the journal *Nature Reviews: Drug Discovery*.¹ The original Nature model, along with subsequent suggested changes, has been used as the basis for an estimation of the optimal length of a branded exclusivity period.²

This appendix describes the Nature model and explains the methodological and conceptual weaknesses that render its results too imprecise and non-robust to inform discussions about the length of a branded exclusivity period. A model that balances the benefits of FOB competition with the costs of potentially forsaking marginal branded drug development projects would be more informative than the Nature model’s approach.³

The appendix is organized as follows: Section I describes the original Nature model’s data inputs and the operation of the model; Section II describes the comments about, suggested changes to, and subsequent sensitivity analysis performed on the original Nature model; Section III describes the current weaknesses with the model; and despite these weaknesses, Section IV presents one correction to the elasticity and internal consistency flaws of the model along with new results based on these corrections.

I. Description of the Nature Model

The Nature model calculates the break-even point for a branded manufacturer’s biologic portfolio as the point at which the net present value of the cumulative cash flows of the portfolio equals zero. The stream of cash flows upon which this calculation is based has the following six components.

¹ Henry Grabowski, *Follow-on Biologics: Data Exclusivity and the Balance Between Innovation and Competition*, 7 NATURE REVIEWS DRUG DISCOVERY 479 (June 2008) [hereinafter “NATURE”].

² Subsequent calculations and adjustments to the Nature model include: Henry Grabowski *et al.*, *Updating Prior Analyses and Responding to Critiques*, DUKE UNIV. DEPT. ECON. WORKING PAPER, No. 2008-10 (Dec. 22, 2008) (hereinafter “Updating Analyses”); Matrix Global Advisors Comment (12/22/08); Alex Brill, *Proper Duration of Data Exclusivity for Generic Biologics: A Critique*, MATRIX GLOBAL ADVISORS, LLC, WHITE PAPER (2008).

³ Such an approach would require, at a minimum, R&D cost information to which the FTC does not have access.

A. Total Pre-Approval Research and Development Costs per Approved Biologic Drug

The first input of the Nature model is an estimate of the pre-approval R&D costs per approved biologic drug based on work by DiMasi and Grabowski.⁴ The original Nature model and subsequent calculations rely on estimates of the total R&D costs for a typical investigational drug, adjusted for the probability of FDA approval, to calculate an estimate of the total R&D costs for a FDA-approved branded biologic drug. The R&D cost estimates are based on the proprietary data for 17 biologic drugs. The cost estimates are the weighted average costs in each phase of development (*i.e.*, preclinical, Phase I, Phase II, and Phase III) across the 17 drugs, where the weights are the probabilities of entering each phase.⁵ The estimated real (*i.e.*, in 2005 dollars) costs for each phase are: \$59.88 million (preclinical), \$32.28 million (phase I), \$31.55 million (phase II), and \$45.26 million (phase III). These costs would be spent over an average 13 year period prior to approval, so that the future value of these costs at the time of approval (using a discount rate of 11.5%) is \$374.70 million.

Because every molecule developed is not approved (*e.g.*, clinical testing may show that it is not safe and/or effective), the total R&D estimate is adjusted for the probability of success. The R&D cost per investigational molecule is converted to an estimate of the R&D cost per *approved* molecule by dividing the \$374.70 million by the estimated probability of success (30.2%). The overall estimate of the total pre-approval R&D costs at launch (using a discount rate of 11.5%) for a typical approved biologic drug is \$1.24 billion. Using a discount rate of 12.5%, the estimate of pre-approval R&D costs is \$1.33 billion.

B. Launch and Plant Transition Costs

The second input of the Nature model is an estimate of the costs of launching production of the new drug. The Nature model and subsequent calculations assumed that the branded manufacturer will spend \$25 million over the two years prior to launch to convert existing manufacturing capacity to the production of the new drug.⁶ It is also assumed that the branded manufacturer will incur additional “launch-related expenditures equal to 10% and 20% of first year’s sales” in the two years prior to launch, respectively.⁷ Using a discount rate of 11.5%, the future value of these costs at the time of launch is roughly \$70 million. Therefore, if the discount rate is assumed to be 11.5%, the typical branded biologic firm is estimated to be “in the

⁴ Joseph DiMasi & Henry Grabowski, *The Cost of Biopharmaceutical R&D: Is Biotech Different?*, 28 MANAG. DECIS. ECON. 469 (2007).

⁵ The phase probabilities, as well as the development times, are estimated from a separate database of 522 biologic drugs.

⁶ Grabowski, NATURE, at 483, Note 6, Box 3.

⁷ *Id.* at 483, Note 9, Box 3.

hole” roughly \$1.31 billion per approved new drug at the time of launch (\$1.24 billion plus \$70 million based on a 11.5 % discount rate).

C. Post-Approval R&D Costs

The third input of the Nature model is an estimate of the costs for post-approval R&D of new indications and formulations. The Nature model and subsequent calculations assumed that these costs are \$24.5 million per year for the first 8 years after approval based on post-approval R&D expenses of traditional small-molecule drug companies.

D. Revenues

The fourth input of the Nature model is an estimate of the revenue stream used to recover the pre-approval R&D costs, launch and transition costs, and post-approval R&D costs. The Nature model’s revenue estimates are based on revenues from a sample of 30 biotechnology drugs. The 30 drugs are ranked into quintiles and the mean amounts for the top four ranked quintiles are then used to calculate the average revenue profile for a typical branded biologic drug. The Nature model excluded the bottom quintile because these drugs “may not have representative R&D cost profiles.”⁸

The timing of the revenues for the hypothetical portfolio is assumed to match that of the “average new drug introduction in the 1990s.” After the maximum revenues are achieved in the tenth year after launch, revenues are assumed to decline by 3.5% per year due to “obsolescence and therapeutic class competition.”⁹ The revenue stream represents worldwide sales and is denominated in 2005 dollars.¹⁰

E. Contribution Margin

The fifth input of the Nature model is an estimate of the operating profit margin, or contribution margin, of the brand drug. After the brand drug is launched, its revenues cover its operating costs each year with the remaining operating profit contributing to the recoupment of the investment costs. The original Nature model assumes that the contribution margin for the biologic portfolio is -30% in the first year after launch, +20% in the second year after launch, and +50% thereafter. The steady-state 50% margin is used because it is “in line with the contribution margins realized by the eight largest biotechnology firms with multiple products on the market.”¹¹

⁸ *Id.* at 485.

⁹ *Id.*

¹⁰ *Id.* at 486.

¹¹ *Id.* at 486.

F. Discount Rate/Cost of Capital

The final input of the Nature model is an estimate of the cost of capital for a biologic drug, *i.e.*, the rate of return required by investors to compensate for the risk involved in developing the brand drug. The original Nature model uses two rates to “capitalize forward” the R&D cost stream to the launch date and discount the profit stream back to the launch date: 11.5% and 12.5%. These rates are justified as “reflective of the equity cost of capital for larger publicly listed biotechnology firms with multiple products on the market in recent periods.”¹² These rates are based on estimates of the real cost of capital over time for an unspecified sample of biotech firms calculated in previous research using the capital asset pricing model (12.5% in 1994, 12.0% in 2000, and 10.0% in 2004).¹³ The original Nature model uses the average (11.5%) and maximum (12.5%) of these three rates in its calculations.

These six components are used to calculate the point at which R&D costs are recouped through post-approval cumulative profits as shown in Table 1 below (which assumes a discount rate of 11.5%). The typical biologic product starts out at launch \$1.31 billion “in the hole.” During each year after launch, it earns an operating profit (assumed to be negative in the first year) which is its contribution margin times its revenue (minus any post-approval R&D). To properly compare profits in different years, this profit stream is discounted back to the launch date. If 11.5% is used as the discount rate, the cumulative profit stream covers the initial R&D expenditures late in the 13th year after launch (*i.e.*, 12.9 years after launch).¹⁴ If 12.5% is used as the discount rate, this break-even point occurs 16.2 years after launch.

Based on these two calculations, Grabowski concludes that the exclusivity period for a branded biologic should last 12 and 16 years after launch: “entry through abbreviated filings should be delayed until the representative NBE [New Biologic Entity] has had the opportunity to earn risk-adjusted break-even returns.”¹⁵

¹² *Id.*

¹³ DiMasi, *The Cost of Biopharmaceutical R&D*, at 474.

¹⁴ Grabowski, *NATURE*, at 486.

¹⁵ *Id.* at 487.

Table 1: Break-Even Analysis w/ Discount Rate = 11.5% (all amounts in millions)

Year	R&D	Revenue	Margin	Post-approval R&D	Launch/Plant	Profit	NPV Profit	Cumulative NPV
0	-\$1,243					-\$1,313	-\$1,313	-\$1,313
1		\$128	-0.3	-\$24.5		-\$63	-\$60	-\$1,372
2		\$243	0.2	-\$24.5		\$24	\$20	-\$1,352
3		\$328	0.5	-\$24.5		\$140	\$106	-\$1,245
4		\$413	0.5	-\$24.5		\$182	\$124	-\$1,121
5		\$506	0.5	-\$24.5		\$229	\$140	-\$981
6		\$577	0.5	-\$24.5		\$264	\$145	-\$836
7		\$648	0.5	-\$24.5		\$300	\$148	-\$688
8		\$676	0.5	-\$24.5		\$314	\$139	-\$550
9		\$713	0.5			\$357	\$141	-\$409
10		\$713	0.5			\$357	\$127	-\$282
11		\$688	0.5			\$344	\$110	-\$172
12		\$664	0.5			\$332	\$95	-\$77
13		\$641	0.5			\$320	\$82	\$5
14		\$618	0.5			\$309	\$71	\$76
15		\$597	0.5			\$298	\$62	\$138
16		\$576	0.5			\$288	\$53	\$191
17		\$556	0.5			\$278	\$46	\$237

II. Summary of Comments

Commenters raised several issues about the inputs, the operation of the model, and the inferences that can be drawn from the model. Alex Brill arrived at different results by varying some of the model's assumptions.¹⁶ First, he suggested that 10% is a more accurate estimate of the cost of capital for biotech firms, rather than 11.5% or 12.5%.¹⁷ Second, he posited that 60%, rather than 50%, is a more accurate estimate of the contribution margin for a large biotech firm.¹⁸ Using these assumptions, he calculates a break-even point nine years after FDA approval of the branded biologic drug.

Brill also explained that the break-even point should not be used as a proxy for the optimal exclusivity period because a branded biologic product is likely to continue earning positive profits even after FOB entry.¹⁹ If exclusivity is granted so that no FOBs can enter until the average branded manufacturer has recouped its R&D costs, then the branded manufacturer will earn "profits that exceed the required rate of return expected by investors."²⁰ If true, this

¹⁶ Brill, *Proper Duration of Data Exclusivity*.

¹⁷ *Id.* at 8 (citing DiMasi, *The Cost of Biopharmaceutical R&D*).

¹⁸ *Id.* at 8-9 (citing an alternate source of financial data more recent than that used in the Nature model).

¹⁹ *Id.* at 10.

²⁰ *Id.*

could lead to consumer harm through the delay of FOB entry. As an illustration, Brill used the 10%/60% discount rate/margin assumptions, along with assumptions from the Congressional Budget Office about the market share and price declines that branded biologic drugs are likely to face with FOB entry.²¹ This illustration shows that a branded manufacturer would break-even ten years after approval even if FOB entry occurs in the eighth year after FDA approval of the branded drug.

Another commenter argued that the use of a portfolio approach in estimating the revenue stream may result in an exclusivity period that is too long and overprotects the branded biologic drugs that are most likely to face FOB competition. Although a branded manufacturer and its capital partners may diversify by investing in many investigational drugs (some of which will become very successful and profitable and others that will be approved, but have relatively small revenues), potential FOB entry is only a credible concern for the most successful of these drugs. The portfolio used in any break-even calculation to determine exclusivity periods should only include those drugs for which FOB entry is likely when the period of exclusivity expires. The original Nature model and subsequent calculations exclude only the bottom quintile of biologic drugs when constructing the portfolio. This commenter suggested that drugs with less than \$250 million in sales are unlikely to face FOB competition, thus implying that the bottom two quintiles should be excluded from the break-even calculation, as the drugs in the second lowest quintile have peak sales of \$100 million.²²

Following the roundtable and in response to Brill's critique, Grabowski questioned Brill's assumption about total market revenues when FOBs enter the market; cited additional research suggesting that the true cost of capital may be higher than originally presented in the Nature model; suggested that the true contribution margin may be lower than originally presented; and provided additional analysis showing how relaxing other assumptions in the model would lead to longer break-even times.²³

Brill also provided post-roundtable comments that included additional alternative interpretations of CBO's assumptions regarding branded manufacturer market share declines following FOB entry.²⁴ In addition to his original calculation (which assumes total market revenues do not change), he presented additional break-even calculations that assume a perfectly inelastic demand. One of these assumes a steady-state price decline of 40% as before and the other assumes a steady-state price decline of 20%. A final calculation assumes no price decline and simply a loss of market share to the FOB entrant. As in his original analysis, all of these

²¹ Congressional Budget Office ("CBO"), Cost Estimate (S.1695), *Biologics Price Competition and Innovation Act of 2007 S. 1695, As Ordered Reported by the S. Comm. on Health, Education, Labor, and Pensions on June 27, 2007* (June 25, 2008), available at <http://www.cbo.gov/ftpdocs/94xx/doc9496/s1695.pdf>.

²² Zuckerman Spaeder Comment (12/22/08) at 10.

²³ Grabowski, *Updating Analyses*, at 13.

²⁴ Matrix Global Advisors Comment (12/22/08).

calculations assume seven years of branded exclusivity, a contribution margin of 60%, and a cost of capital of 10%. With these assumptions, he finds that the branded manufacturer breaks-even nine to 14 years after launch.

Finally, one commenter surmised that the Nature model was “fraught with peril.” He suggested that: “Aside from a possibly nonrepresentative sample, the exercise involves numerous assumptions about the cost of capital, profit margins, and prices after the first follow-on enters the market. Reasonable changes to these assumptions can easily affect the results by 30–40 percent.”²⁵

III. Problems with the Break-Even Model - Analysis

The problems with the Nature model fall into three types: (1) problems with the “inputs” to the model (*i.e.*, problems with the underlying components); (2) problems with the incorporation of FOB entry into the model after a period of exclusivity; and (3) problems with the interpretation and use of the results.

A. Problems with the Input Assumptions

The first input to the Nature model is the estimate of pre-approval R&D costs for a representative biologic drug. The problem with this estimate is that it is based on a sample of only 17 drugs. No variance information is presented for the sample.²⁶ Unless the R&D costs within each clinical phase are essentially identical across the drugs, it is likely that the confidence interval around the R&D cost estimate is large and, thus, the R&D cost estimate is less likely to be accurate. Further, 13 of the 17 drugs were developed by one firm and the sample is restricted to therapeutic recombinant proteins and monoclonal antibodies, so it is possible that the sample is non-random and not representative of biologic drugs overall.

Another important input into the model is the revenue stream of the representative biologic drug. There are two potential problems with the revenue stream used in the Nature model.²⁷ First, the revenue stream includes sales from post-approval indications and formulations in addition to the original indication/formulation.²⁸ The revenue stream associated with the original indication/formulation is not provided, so one cannot calculate the break-even point of the original indication/formulation with the data in the model.

²⁵ American Enterprise Institute Comment (12/10/08) at 6.

²⁶ DiMasi, *The Cost of Biopharmaceutical R&D*.

²⁷ The FTC was unable to determine how the Nature model factors in sales of biologic products outside the United States, including potential sales of biologic products in European markets prior to their approval in the U.S., and European market revenues for the pioneer’s branded product after biosimilar entry. Accordingly, there could be additional weaknesses in the Nature model concerning its treatment of international revenues.

²⁸ Grabowski, *NATURE*, at 483, Box 3, Note 5.

Second, the revenue stream assumes “therapeutic class competition.”²⁹ The time frame of the therapeutic class competition is not stated in the original Nature model, but Grabowski’s post-conference comment suggests that the therapeutic class competition is assumed to begin in the tenth year after approval of the brand drug.³⁰ Thus, the original Nature model implies that a “first-in-class” branded drug will recoup its R&D costs even if therapeutic class competition occurs. And because entry of FOBs is likely to have the same market effect as entry by branded competitors, this assumption leads to the conclusion that the branded exclusivity period for the first-in-class branded drug should be less than 12 to 16 years.

In addition, like the R&D cost estimates, the revenue estimates are based on a small sample. The model relies on 24 biologic drugs to estimate the revenue stream. These are the drugs in the top four quintiles of the distribution and the spread in average peak revenues between the top and second-to-bottom quintiles (\$2 billion to \$100 million) suggests a large variance in this distribution. Like the R&D cost estimates, it is likely that the confidence interval around the estimated revenue stream is large and, thus, the revenue estimates are less likely to be accurate. In addition, it is unknown whether the 24 drugs are a random sample of biologics. If not, or if they substantially overlap with the 17 drugs used to estimate the R&D costs, the revenue estimates may be biased like the R&D cost estimates.

Furthermore, an implicit assumption of the Nature model is that there is no correlation between R&D costs and revenues, so that an average R&D cost stream and an average revenue stream can be used to make inferences about average profitability. However, R&D costs and revenues may be positively or negatively correlated, making the variance of the profit estimates smaller or larger, respectively, than suggested by independent samples. Since the samples used to estimate R&D costs and revenues are not disclosed, it is impossible to determine if this ameliorates or exacerbates the measurement error.

Another important component in the model is the assumed cost of capital. Despite the disagreement over the appropriate cost of capital for a biologic firm, the model assumes a constant cost of capital throughout the entire product life cycle. Investments in biologic R&D during the early stages of research (*e.g.*, preclinical R&D) might have a higher cost of capital reflecting their relative risk, while investments during the later stages (*e.g.*, phase III and post-approval) might have a lower cost of capital reflecting the relative certainty of the return.³¹ As a result, this could substantially change the total capitalized amount to be recouped.

²⁹ *Id.* at 485.

³⁰ Duke University Comment (12/22/08) at 5 (“Specifically, in the Nature article I assume that, starting ten years following launch of the innovator biologic, revenues will begin to decline due to obsolescence at a rate of 3.5% per year. The introduction of new branded biologics by competitors (branded competition with other “first generation” and “second generation” products) is a likely source of this obsolescence.”).

³¹ See *e.g.*, Office of Technology Assessment, United States, Congress Edition, *Pharmaceutical R&D: Costs: Risks and Rewards*, (1994) at 66.

Apart from the estimation errors associated with the R&D cost and revenue inputs and the cost of capital assumptions, it is unclear whether the use of sample means or a portfolio approach is appropriate. The samples of drug projects used to create the R&D cost and revenue estimates are biologic development projects that were actually pursued. At least initially, all of these projects were perceived as potentially profitable ventures or else they would not have been funded. Introducing a FOB pathway might make some of these formerly profitable projects unprofitable. If the R&D cost and revenue figures are independent, the use of sample means in the Nature model imply that the exclusivity period should be set so that development of projects that are above the profit mean continue to be pursued while those below the profit mean are abandoned. If the R&D cost and revenue estimates are not independent (*e.g.*, more expensive projects are associated with larger expected sales), it is not clear which projects would be abandoned with a FOB pathway determined using the R&D cost and revenue mean estimates. A better approach to determining the optimal length of a branded exclusivity period would balance the benefits of FOB competition with the costs of potentially forsaking marginal branded development projects.

B. Problems Incorporating FOB Entry into the Break-Even Model

The versions of the model that explicitly incorporate FOB entry contain two questionable assumptions that may bias the results. First, in most of the calculations that incorporate FOB entry, it is assumed that the price of the branded drug will gradually decline after FOB entry so that it is 40% below its pre-FOB price in four years. This assumption corresponds roughly to the CBO's assumption that the FOB price will be 40% less than the pre-FOB branded price four years after entry. Of course, the latter does not necessarily imply the former, as it is theoretically possible for the FOB's price to be 40% less than the branded drug's pre-FOB price even if the branded drug's price falls by more or less than 40%.

The assumption that the branded drug price will match the FOB price represents the least profitable scenario for the branded manufacturer: the scenario in which the branded drug and the FOB are perfect substitutes.³² Still, the 40% branded price decrease assumption is ad hoc and is not necessarily consistent with the CBO assumption that the branded drug's market share will eventually decline by 35%. In the calculations of Grabowski and Brill, competition between the branded manufacturer and the FOB firm following FOB entry is not modeled explicitly. It is reasonable to expect that the branded drug's price decrease and market share decrease are inter-related and are jointly determined. In other words, the assumption that the branded drug's share declines by 35% in large part determines what price decreases are possible. The analysis below provides one example of how the Nature model can be corrected to account for this relationship.

The second questionable assumption concerns overall revenues after FOB entry. In some variations of the model, it is assumed that overall market revenues stay the same after FOB entry. In other words, it is assumed that the branded manufacturer faces a demand for its drug that is unitary elastic so that price decreases and the resulting increases in the quantity demanded

³² Matrix Global Advisors Comment (12/22/08) at 3 ("Given the desire to impose conservative assumptions, the Brill model assumes the price decline of innovator drugs is equal the FOB price.").

exactly offset producing no change in overall market revenue. For profit-maximizing firms, this is impossible as profit-maximizing firms (with positive marginal costs) always price in the elastic portion of the demand they face.

In other variations of the model, it is assumed that overall revenues decline by the same fraction as the price which is equivalent to assuming that the demand for the branded drug is perfectly inelastic (*i.e.*, a price decline results in no change in the quantity produced and sold). A profit-maximizing firm facing a perfectly inelastic demand will increase its price to infinity, as it can sell the same amount at a higher and higher price. This result also is impossible. Branded manufacturers set prices in the elastic portion of the demands they face for the drugs they produce, as do all profit-maximizing firms.³³

This latter assumption is problematic because it assumes away the primary benefit of establishing an abbreviated pathway for follow-on biologics, namely, to reduce the price of biologic drugs so more people can have access to them. Furthermore, this assumption of inelastic demand directly contradicts the contribution margins used in the model. The Lerner Index dictates that for any profit-maximizing firm, its profit margin over marginal cost will equal the inverse of (the absolute value of) the price elasticity of demand for the demand the firm faces for its product. This condition holds for all profit-maximizing firms, not just monopolists, as it is derived from the first-order necessary condition for profit-maximization. Thus, any profit-maximizing firm that has positive marginal costs and a finite, positive margin over marginal cost must be facing an elastic demand (at least locally around the profit-maximizing price). The contribution margins used in the model are not necessarily equal to the margins over marginal cost used in the Lerner Index (*e.g.*, they may include some overhead costs). However, the assumption of finite contribution margins necessarily implies finite margins over marginal cost and, thus, demand that is elastic, not perfectly inelastic. Below, we correct the model's calculations using the Lerner Index with the contribution margin serving as a proxy for the margin over marginal cost.

C. Problems in the Interpretation and Use of the Results

Apart from the problems with the underlying assumptions of the model, the results of the model are prone to misinterpretation. First, the inclusion of post-approval R&D costs and revenues in the break-even analysis makes it easy to misinterpret the results if one is using the analysis to determine the extent of the exclusivity period for branded biologics. If a fixed exclusivity period is set to recoup the costs of pre-approval and post-approval R&D, then the exclusivity period provides no marginal incentive to the branded firm to conduct post-approval R&D.

Theoretically, the preceding issue could be resolved if one were able to separate the revenues from post-approval indications and formulations from the revenues for the original indication and formulation. However, even if one were able to correct this problem and all of

³³ Dennis W. Carlton and Jeffrey M. Perloff., MODERN INDUSTRIAL ORGANIZATION, at 93 (4th ed. 2005).

the previous problems, a more fundamental problem with the general model remains: small changes in the input assumptions yield large swings in the resulting break-even period.

This last point can be illustrated by considering Grabowski's post-conference comment that the actual cost of capital for biotech firms may be as high as 13-15%. Recall that the Nature model originally found that a representative biologic portfolio would break even in the 13th year if the cost of capital was 11.5% and would break even in the 17th year if the cost of capital was 12.5%. Using identical assumptions to the original Nature model, but increasing the cost of capital to 13.25% produces a break-even point in the 23rd year. If the cost of capital is greater than or equal to 13.7%, and all of the other assumptions in the original model are retained (including no FOB entry at any point), the representative biologic portfolio *never* breaks even. The fact that the representative biologic portfolio *never* breaks even when using a cost of capital greater than or equal to 13.7%, even though Grabowski's post-roundtable comments suggest 14-15% is a plausible cost of capital for biotech firms, casts doubt on the accuracy and reliability of the model.

IV. Correcting Problems in the Nature Model Does Not Improve Its Usefulness

As discussed above, the break-even calculations of the Nature model suffer from many problems. Some of these problems can be corrected. In particular, the assumptions of unitary elastic and perfectly inelastic demand can be discarded to make the model's elasticity assumptions consistent with its contribution margin assumptions. Second, the model's consistency problems in the post-FOB world can be corrected by applying a reasonable and flexible competition model. The corrections described below are not exhaustive and simply represent one way these problems can be addressed. In fact, the assumption of Cournot FOB/branded competition is likely wrong, but is a reasonable approach that is consistent with the assumption made by both Grabowski and Brill that the FOB and branded drugs will have the same price after FOB entry. However, the corrections illustrate that the elasticity and consistency problems are not innocuous, but instead have a significant impact on the results. These corrections do not address the more fundamental problems of imprecision and non-robustness. As such, even with these corrections, we find the break-even framework uninformative in the debate about proper exclusivity periods for branded biologic drugs.

First, regarding the elasticity assumption, assume that the contribution margin of the branded manufacturer is equal to the branded manufacturer's margin over marginal cost $(p - mc)/p$. These two margins are probably not equal, as the former includes some overhead costs, but the contribution margin is the best proxy for the margin over marginal cost that is readily available. From the Lerner Index, the price elasticity of demand for the branded manufacturer's drug is (-1 times) the inverse of the contribution margin. In other words, the assumption of a contribution margin of 50% implies an elasticity of -2 and a contribution margin of 60% implies an elasticity of -5/3. Let the subscript 1 denote the period before FOB entry and let the subscript 2 denote the period after FOB entry. Following Grabowski and Brill, we assume that the branded drug's price following FOB entry is the same as the FOB's price.³⁴ Let α be such that p_2

³⁴ This is likely a conservative assumption as the branded manufacturer may be able to price above the FOB and any

$=\alpha p_1$. For example, a steady-state price decline of 40% following FOB entry implies that $\alpha = 0.6$. The price elasticity of demand (ε) is the ratio of the percentage change in quantity with a corresponding percentage change in price. Using an approximation of the elasticity and normalizing $q_1 = 1$, this implies:

$$(1) \quad \varepsilon = \frac{\frac{q_2 - q_1}{q_1}}{\frac{p_2 - p_1}{p_1}} \Rightarrow q_2 = \varepsilon(\alpha - 1) + 1$$

This implies that the total market (*i.e.*, branded + FOB) revenue after FOB entry is:

$$(2) \quad R_2 = p_2 q_2 = \alpha[\varepsilon(\alpha - 1) + 1]R_1$$

The profit-maximizing branded manufacturer's marginal cost will equal its marginal revenue before FOB entry:

$$(3) \quad mc = mr = p_1 \left(1 + \frac{1}{\varepsilon} \right)$$

Therefore, assuming the branded manufacturer's marginal cost does not change after FOB entry, the branded manufacturers's post-FOB margin will be:

$$(4) \quad \frac{p_2 - mc}{p_2} = \frac{\alpha - \left(1 + \frac{1}{\varepsilon} \right)}{\alpha}$$

Second, a model of the competition between the branded firm and the FOB entrants is needed to characterize prices and market shares that are consistent with each other. There are a number of models that could be used, but the Cournot model seems most appropriate in the current context for the following reasons:

- All versions of the Nature model that incorporate FOB entry assume that the branded firm and the FOB will have the same price after FOB entry. This assumption is likely incorrect as it is likely that the brand and FOBs will not be perfect substitutes and the brand may continue to price higher than the FOBs. However, this assumption is used because it represents the least profitable scenario for the branded manufacturer.

ability to do so likely would allow the branded manufacturer to break-even sooner.

- Most analysts expect that the price of biologics will decline as more FOBs enter, which is a characteristic of the Cournot model.³⁵
- The Cournot model is flexible and requires limited assumptions to implement. It is robust across most types of demand and cost functions. Other potential models (e.g., differentiated Bertrand) require more assumptions to implement. However, if feasible to implement, a monopolistic competition model would be more accurate, as it would capture the differentiation between the brand drug and the FOB that is likely to characterize competition after FOB entry.

The Cournot analogue to the Lerner Index dictates that a firm's margin over marginal cost will equal (the absolute value of) the inverse of the price elasticity of demand times the firm's market share. Therefore, after FOB entry, the branded manufacturer's margin is:

$$(5) \quad \frac{p_2 - mc}{p_2} = -\frac{s}{\varepsilon}$$

where s is the branded manufacturer's market share. Substituting the branded manufacturer's marginal cost as calculated in (3) above, we can solve for the branded manufacturer's post-FOB price as a function of the branded pre-FOB price:

$$(6) \quad \frac{p_2 - \left[p_1 \left(1 + \frac{1}{\varepsilon} \right) \right]}{p_2} = -\frac{s}{\varepsilon} \Rightarrow p_2 = \frac{(\varepsilon + 1)}{(\varepsilon + s)} p_1$$

In other words, if the competition between the branded firm and the FOB firms is consistent with the Cournot model, assumptions about the brand's pre-FOB margin (which determines ε) and the brand's post-FOB market share uniquely determine the brand's price decrease after FOB entry. The CBO's assumption of a steady-state market share decline of 35% and the assumption of a 50% margin imply a 26% branded manufacturer price decrease. If a 60% margin is used instead, the branded manufacturer's price decrease is roughly 34%. Using these values in the break-even calculations produces the following break-even times:

³⁵ See, e.g., Alexis Ahlstrom et al., *Modeling Federal Cost Savings of Follow-On Biologics*, Avalere Health LLC (Mar. 2007) available at http://www.avalerehealth.net/research/docs/Follow_on_Biologic_Modeling_Framework.pdf.

Table 2: Year After Launch in Which Branded manufacturer Breaks-Even (Data Exclusivity = 7 Years)

Margin/Cost of Capital	Lerner ($\epsilon = -1/\text{margin}$); 35 % share decline; Cournot competition	Unitary elasticity; 35 % share decline; 40 % price decline	Perfect inelasticity; 35 % share decline; 40 % share decline
50%/10%	14	Never	Never
50%/11.5%	34	Never	Never
50%/12.5%	Never	Never	Never
60%/10%	10	11	14
60%/11.5%	14	17	Never
60%/12.5%	24	Never	Never

When the elasticity assumption is corrected and the price and share declines are made internally consistent, the results are much different than in previous versions of the Nature model. For example, Grabowski concludes that “notably, with an exclusivity period of 7 years, the *only* combination of assumptions that yields a breakeven point of less than 50 years is the one used by Brill.”³⁶ On the contrary, with an exclusivity period of seven years, there is only one set of assumptions (of those most commonly used) that does not result in the branded manufacturer breaking-even.

However, even when the elasticity assumption is corrected and the price and share declines are made internally consistent, the break-even period varies from 10 years to infinity. Small changes to the margin and cost of capital assumptions cause large swings in the results. Under the original assumptions of a 50 % margin and a 11.5 % cost of capital, the brand biologic breaks even after 34 years if the exclusivity period is seven years. Increase the cost of capital assumption to 13.7 % and the brand would *never* recoup its investments, even if exclusivity were perpetual and FOB’s *never* entered. Note also that these large swings in the results occur even when one assumes the underlying cost and revenue estimates are measured without error. If one were to incorporate the large estimation errors that likely exist because of the small samples on which the estimates are based, the range of plausible results would only expand. A model that produces such vastly different results with small and reasonable changes in the underlying assumptions is unreliable as a basis for policy.

³⁶ Grabowski, *Updating Prior Analyses*.

APPENDIX B

I. FDA's Drug Approval Processes

The Food and Drug Administration ("FDA") approves prescription drug medicines for marketing in the United States through two separate and distinct product approval pathways, depending on the drug's method of manufacture. The first pathway applies to small molecule drugs and the second pathway applies to biologic drugs.

Small molecule drugs are manufactured by chemical synthesis. The FDA's Center for Drug Evaluation and Research ("CDER") approves small molecule drugs pursuant to the Federal Food, Drug, and Cosmetic Act ("FD&C Act").¹ To obtain FDA approval, the small molecule drug manufacturer, or company sponsor, must complete the requirements of a full New Drug Application ("NDA"), including a showing of medical benefit over patient risk.²

Biologic products are derived from living matter (*e.g.*, purified from blood) or manufactured in living cells (*e.g.*, yeast, *e.coli*, or mammalian cells) using recombinant DNA biotechnologies.³ The FDA's Center for Biologics Evaluation and Research ("CBER") approves biologic drugs for marketing pursuant to the Public Health Safety (PHS Act).⁴ To obtain FDA approval, the company sponsor must complete the

¹ 21 U.S.C.A. § 301 *et seq.* (2009).

² A full NDA is also known as a 505(b)(1) application, referring to FD&C Act § 505(b)(1). 21 U.S.C.A. § 355(b)(1) (2009).

³ Although biologics must be approved through the BLA process, which center at the FDA performs the review is more complicated. CBER regulates allergenic extracts (*e.g.*, for allergy shots and tests), blood and blood components, gene therapy products, devices and test kits, human tissue and cellular products used in transplantation, and vaccines. The FDA transferred review of all recombinant proteins and monoclonal antibodies, except for hormones such as human growth hormone and insulin, to CBER. Then in 2003, the FDA transferred certain therapeutic biologic products from CBER to CDER. FDA, *Transfer of Therapeutic Products to the Center for Drug Evaluation and Research* available at <http://www.fda.gov/cber/transfer/transfer.htm>. Accordingly, CDER regulates monoclonal antibodies designed as targeted therapies in cancer and other diseases, cytokines (types of proteins involved in immune response), growth factors (proteins that affect the growth of a cell), enzymes (types of proteins that speed up biochemical reactions), such as thrombolytics (used to dissolve blood clots), immunomodulators (agents that affect immune response). Additionally cell therapies and gene therapies are reviewed by the FDA's Cellular, Tissue and Gene Therapies. 42 U.S.C.A. § 262 (2009).

⁴ FDA's broad regulatory authority over biologic issues, including approval of biologic drug products resides in the PHS Act. The PHS Act also provides the FDA with the authority to: (a) protect the public against threats of emerging infectious diseases, (b) to promote the safe and appropriate use of biological products, (c) inspect manufacturing facilities of biologics before product approval is granted, and thereafter, on a regular basis, (d) monitor the safety of biological products after they are marketed (e) suspend biologic licenses where there exists a danger to public health, (f) prepare or procure products in the event of shortages and critical public health needs, and (g) prevent the introduction or spread of communicable diseases within the country. FDA, *Frequently Asked Questions About Therapeutic Biological Products*, available at <http://www.fda.gov/cder/biologics/qa.htm>.

requirements of a Biologics License Application (BLA). The FD&C Act also regulates biologic products because most biologic products also meet the FD&C Act's definition of "drugs".⁵

The small molecule and biologic pathways have one main difference: the FDA may approve generic small molecule drugs using an abbreviated pathway, but no abbreviated process exists for follow-on biologic drugs.

A. New Drug Approvals

Although new small-molecule drug applicants file an NDA and new biologic drug applicants file a BLA, the development and regulatory approval process is similar for both categories.⁶ For example, both small molecule and biologic drug applicants must establish medical benefit over patient risk.⁷ The applicant, or company sponsor, also must prove the product is safe and effective. To do so, the applicant submits an NDA or BLA that contains the following information: (a) preclinical analytical tests, preclinical studies, and formulation studies; (c) an Investigational New Drug Application ("IND") to initiate human clinical testing; (d) adequate and well-controlled human clinical trials to establish the safety and efficacy of the drug for its intended use; (e) approval and validation of manufacturing facilities used in production of the pharmaceutical product; (f) drug manufacture and analytical methods; and (g) proposed product packaging and labeling.⁸

The preclinical phase of any new drug development typically begins with assays and large scale screening of compounds against targets of interest. Once a lead

⁵ FD&C Act defines "drug" as "(B) articles intended for use in the diagnosis, cure, mitigation, treatment or prevention of disease in man or animals; (C) articles (other than food) intended to affect the structure or any function of the body of man or other animals; and (D) articles intended for use as a component of any article specified in clause (A), (B), or (C)." 21 U.S.C.A. § 321(g)(1) (2009). For historic reasons, recombinant human insulin and recombinant human growth hormone ("HGH") were approved under section 505 of the FD&C Act, not under the PHS Act. See FDA, *FDA 101: Biological Products*, available at <http://www.fda.gov/-consumer/updates/-biologics062608.html>; see generally, FDA's Center for Biologic Drug Evaluation ("CBER") webpage, available at <http://www.fda.gov/cber/about.htm>.

⁶ See FDA's Center for Drug Evaluation and Research ("CDER") webpage, available at <http://www.fda.gov/cder/biologics/qa.htm>; see also FDA, *The New Drug Development Process: Steps from Test Tube to New Drug Application Review*, available at <http://www.fda.gov/cder/handbook/develop.htm>.

⁷ Behrman at 17, 19 ("the [FDA's] review of any application, be it drug, be it a biological product, makes an assessment of what is in the best interest of the public given the available information. There will always be uncertainty. There is uncertainty about the simplest small molecule drugs."); see *id.* ("Although medical products are required to be safe, safety does not mean zero risk, since all medical products are associated with some level of risk. A safe biological product is one that has reasonable risks, given the patient's condition, the magnitude of the benefit expected, and the alternatives available. The choice to use a biological product involves balancing the benefits to be gained with the potential risks.").

⁸ See 42 U.S.C.A. § 262; 21 U.S.C.A. § 321 *et seq.*; and 21 C.F.R. 601.2.

compound is isolated, preclinical safety trials are conducted, as well as trials in predictive animal models. This preclinical phase typically takes one to five years.⁹ After preclinical tests are completed, a drug sponsor submits the results in an IND to the FDA for approval before human clinical trials begin.

Human clinical trials typically consist of three phases. In Phase I clinical trials, a small group of healthy human patients are given the drug to determine if the drug is safe in humans.¹⁰ In Phase II clinical trials, a small sample of the intended patient population are given doses of the drug to provide a preliminary assessment of the efficacy of the drug for a specific clinical indication, find dose tolerance, and determine the optimal dose range. Safety data also is collected in Phase II as it is in all phases of drug testing.¹¹ Phase III studies are initiated if Phase I and Phase II studies indicate the drug is safe, and has some efficacy in the targeted patient population. Phase III clinical trials are designed to gather sufficient data in a broad target population in order to establish safety and efficacy for a particular indication.¹²

The time needed to conduct these trials varies based on factors such as indication, availability of reliable biomarkers to measure efficacy, patient size, and ease of patient accrual. Phase I trials generally take one to two years. Phase II trials, including a full dose ranging study take two to three years. Phase III trials are the longest, taking approximately three to five years. Time variability, however, is significant as efficacy burdens vary. For example, it takes less time to collect the data using an accepted biomarker, such as blood cell levels, to measure efficacy of a treatment than it does for to collect data measuring disease free progression, mortality and morbidity data. Drug products also are subject to marketing exclusivities, described in more detail below.

B. Abbreviated Drug Approvals for Follow-on and Generic Products

Prior to 1984, no process existed for abbreviated approval of generic small-molecule drugs. Generic versions of drugs approved after 1962 could only be approved pursuant to either a full New Drug Application or a “paper NDA” application under Section 505(b)(2) of the FD&C Act.¹³ As a result, few companies developed generic drugs because of the high cost to perform the required clinical trials.¹⁴

⁹ See e.g., Ernst Berndt, *et al*, *Opportunities for Improving the Drug Development Process: Results from a Survey of Industry and the FDA*, NBER Working Paper No. W11425, (June 2005), available at <http://ssrn.com/abstract=745818>.

¹⁰ See 21 C.F.R. §312.21(a) (2008).

¹¹ *Id.* §312.21(b).

¹² *Id.* §312.21(c).

¹³ See H.R. Rep. 98-857(I), 1984 U.S.C.A.N. 2647; Letter from Janet Woodcock, Director, CDER, FDA to Petitioners (October 14, 2003) at 6, available at <http://www.fda.gov/ohrms/DOCKETS/dailys/03/oct03/102403/03p-0408-pdn0001.pdf> [hereinafter “FDA’s First Response to Omnitrope CPs”]. Generic drugs applications of drugs approved pre-1962 were approved

In 1984, Congress enacted the Hatch-Waxman Amendments to the FD&C Act (“Hatch-Waxman”) which established an abbreviated regulatory pathway to approve generic drug versions of drugs approved under that act. Hatch-Waxman provided the FDA with discretionary authority to not require generic applicants duplicate the safety and efficacy trials of the reference drug. Rather the Hatch-Waxman Act authorized the FDA to rely on its prior findings of safety and efficacy of previously approved drug products when the agency later reviewed the generic drug’s application.¹⁵ The Hatch-Waxman Act reflected Congress’ attempt to balance the need to encourage innovation with the desire to speed the availability of lower cost alternatives to approved drugs.”¹⁶

1. The Section 505(b)(2) “Paper NDA” Pathway

The 505(b)(2) or “paper NDA” pathway is a partially-abbreviated pathway for drugs that are similar to, but not copies of, a reference small-molecule drug. This pathway pre-existed the Hatch-Waxman Act. A 505(b)(2) applicant relies on one or more safety or efficacy investigations that were not conducted by the 505(b)(2) applicant, and for which the 505(b)(2) applicant has not obtained a right of reference, *e.g.*, reliance on results in the published literature. This pathway is especially useful for new dosage forms, strengths, rates of administrations, dosing regimens and new indications.

The 505(b)(2) pathway permits the FDA to rely “to the greatest extent possible on what is already known about a drug” so as to avoid requiring drug sponsors to conduct and submit studies that “are not scientifically necessary.” FDA has stated that many of the drugs approved via the 505(b)(2) route would never have reached the market, or would have been significantly delayed, without this pathway.¹⁷ Indeed, five significant FDA-identified harms could occur without the 505(b)(2) pathway: (1) diversion of industry resources that could otherwise be used to undertake innovative research; (2) increased drug costs; (3) strain on FDA review resources; (4) slowing of the process for drug approval with no corresponding benefit to the public health; and (5) significant ethical concerns raised by requiring duplicative studies that subject human beings and animals to medically and scientifically unjustified testing.¹⁸

pursuant to the Drug Efficacy Study (“DESI”) program upon a showing that they were duplicates of the reference drug. The DESI system was obviated by Hatch-Waxman provisions.

¹⁴ Post-1962 approved drugs whose patents had expired and were available for generic manufacturers, included five best selling drugs: Valium, Motrin, Inderal, Dyazide, and Lasix. *See* H.R. Rep. 98-857(I), 1984 U.S.C.C.A.N. 2647 at 2650; FDA’s First Response to Omnitrope CPs at 6.

¹⁵ 21 U.S.C.A. § 355(j)(2)(A)(ii) – (iv) (2009).

¹⁶ FDA’s First Response to Omnitrope CPs at 2 (citing *Eli Lilly and Co. v. Medtronic, Inc.*, 496 U.S. 661 (1990), *Bristol-Myers Squibb Co. v. Royce Labs, Inc.*, 69 F.3d 1130, 1132-34 (Fed. Cir. 1995)).

¹⁷ *Id.* at 4, citing approximately 80 drug approvals via the 505(b)(2) process.

¹⁸ *Id.* at 3-4; H. REP. 98-857 (1984), *as reprinted in* 1984 U.S.C.C.A.N. 2647, at 2687 (“The only difference between a NDA and an ANDA is that the generic manufacturer is not required to conduct human clinical trials. FDA considers such retesting to be unnecessary and wasteful because the drug has already

2. The 505(j) ANDA Pathway

As discussed above, in 1984, Congress created an abbreviated pathway for approval of generic small-molecule drugs, this also is known as the 505(j) ANDA Pathway. Hatch-Waxman was designed to facilitate competition from lower-priced generic drugs, while maintaining incentives for pharmaceutical companies to invest in developing new drugs.¹⁹ It also gave FDA discretionary authority to review an abbreviated new-drug application (“ANDA”) for generic small molecule drugs.²⁰ This “reflected Congress’ attempt to balance the need to encourage innovation with the desire to speed the availability of lower cost alternatives to approved drugs.”²¹

Under the Hatch-Waxman Act, a generic drug applicant only is required to show that its product includes the same active ingredient(s) and is bioequivalent to a reference drug, but it does not need to replicate the clinical trials and other testing of the reference product.²² This process typically involves bioequivalency trials in healthy human volunteers, showing that a generic drug has the same levels of the same active pharmaceutical ingredient as the reference branded product. Because reference and ANDA drugs must have the same or similar API, dosage forms, strength, route of administration, labeling, quality, performance and intended use duplicate clinical trials are unnecessary. State substitution laws allow for the substitution of a bioequivalent generic product for the branded reference drug at the retail pharmacy without the doctor’s involvement.

3. Patent Restoration and Patent Listings for New Drug Products

Before Hatch-Waxman, 505(b)(2) applicants could not begin preclinical or clinical trials until after patents expired on the relevant branded product without risking infringement of the branded product’s patents. The risk of patent infringement coupled with the FDA generic approval process, in effect, extended the term of the branded company’s patent protection and delayed market entry by follow-on applicants’ versions of branded pharmaceutical drug products.²³ Hatch-Waxman limited the applicant’s

been determined to be safe and effective. moreover, such retesting is unethical because it requires that some sick patients take placebos and be denied treatment known to be effective.”); Behrman at 24-25.

¹⁹ The Federal Food, Drug, and Cosmetic Act, 21 U.S.C.A. § 301 *et seq.*, as amended by the Drug Price Competition and Patent Term Restoration Act of 1984 (the “Hatch-Waxman Act”) and the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, 21 U.S.C.A. § 355(j) and 35 U.S.C.A. § 271(e).

²⁰ 21 U.S.C.A. § 355(j) (2009). See 21 U.S.C.A. § 355(j)(2)(A)(ii)-(iv) (2009).

²¹ FDA’s First Response to Omnitrope CPs at 2.

²² 21 U.S.C.A. § 355(j)(2)(A)(ii) – (iv) (2009).

²³ See FTC GENERIC DRUG STUDY at 7. The “Bolar Amendment” passed as part of the Hatch-Waxman, reversed the Federal Circuit’s decision in *Roche Products, Inc. v. Bolar Pharmaceutical Co.*, 733 F.2d 858

infringement liability so that it could begin the research, development, and manufacture of a drug product intended for FDA approval without infringing the branded product's patents.

Before 1984, branded pharmaceutical companies asserted that the effective terms of the patents covering their drugs were shortened due to the delays in the FDA approval process. To maintain incentives for branded drug product innovation in the face of generic competition, Congress included in the Hatch-Waxman Amendments patent restoration provisions that apply to drugs approved under both the FD&C Act and the PHS Act.²⁴ The extension period is calculated on the basis of length of time required to study and gain approval of the patented product. A maximum of five years can be restored to the patent. In all cases, the total patent life for the product with the patent extension cannot exceed 14 years from the product's approval date, or in other words, 14 years of potential marketing time. If the patent life of the product after approval has 14 or more years, the product would not be eligible for patent extension.²⁵

Additionally, Hatch-Waxman provided operational provisions to encourage simultaneous running of the patent resolution process with any regulatory approval process, including marketing exclusivity periods.²⁶ To accomplish this, Hatch-Waxman amended the FDA's new drug approval process to require that the reference branded company list all of the reference drug's patents, and patent extensions.²⁷ Once these

(Fed.Cir.1984), and provided that "[I]t shall not be an act of infringement to make, use, offer to sell, or sell within the United States or import into the United States a patented invention...solely for uses reasonably related to the development and submission of information [to support a market approval to the FDA]"; 35 U.S.C.A. § 271(e)(1); *Merck v. Integra*, 545 U.S. 193 (2005)(Section 271(e)(1) provides a wide berth for use of patented drugs in activities related to federal regulatory process, including uses reasonably related to the development and submission of any information to the FDA); *Eli Lilly & Co. v. Medtronic, Inc.*, 496 U.S. 661 (1990) (It is not an act of infringement to use or import into the United States patented invention solely for uses reasonably related to the development and submission of information to the FDA for product approvals).

²⁴ See H. REP. 98-857 (1984), as reprinted in 1984 U.S.C.C.A.N. 2647 at 2687; PhRMA, *Delivering on the Promise of Pharmaceutical Innovation: The Need to Maintain Strong and Predictable Intellectual Property Rights*, (April 22, 2002); FTC Generic Drug Study at 7.

²⁵ See 35 U.S.C.A. § 156. See also FDA CDER, *Small Business Assistance: Frequently Asked Questions on the Patent Term Restoration Program*, available at <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/SmallBusinessAssistance/ucm069959.htm>.

²⁶ FDA's First Response to Omnitrope CPs at 6.

²⁷ Section 505 of the Hatch-Waxman Amendments requires an NDA applicant, including some 505(b)(2) applicants, to submit to the FDA (for publication in the Approved Drug Products with Therapeutic Equivalence Evaluations ("the Orange Book")) the identifying all US patents that claim the drug substance, methods of formulating, composition of matter, and of method of using the drug and which could be infringed.

patents are listed in the Orange Book it is incumbent upon the follow-on applicants to certify how these patents relate to its drug product.²⁸

If an ANDA or 505(b)(2) NDA applicant certifies that a referenced drug patent information has not been filed in the Orange Book, or that such patent has expired, then the FDA may approve the application immediately, provided other requirements are met.²⁹ If the applicant certifies that it will not launch its product until after the referenced product's patents expire, the FDA may approve the application effective on the date the patent expires.³⁰ However, if an applicant makes a certification under Paragraph IV, Hatch-Waxman requires that the applicant to also provide notice to both the patent holder and the NDA filer.³¹ Once the ANDA filer has provided such notice, a patent holder (usually the referenced branded company) must bring an infringement suit within 45 days to trigger the 30-month stay of FDA approval of the application. Hatch-Waxman provides a 30-month stay of FDA approval with a detailed statement of the factual and legal basis for the applicant's assertion that the patent is invalid or not infringed. If suit is not filed by that date, the FDA may approve the application. If patent infringement litigation is initiated by the branded product company within the 45-day period, then the FDA approval of the application is stayed until the earliest of: (1) the date the patent(s) expire; (2) a final determination of non-infringement or patent invalidity by a court in the patent litigation; or (3) the expiration of the 30 months from receipt of notice of the paragraph IV certification.³²

4. Marketing Exclusivities

Under the Hatch-Waxman Act, FDA enforces five types of exclusivity: (1) new chemical entity – five years; (2) new clinical investigation – three years; (3) orphan drug – seven years; (4) pediatric – six months; and (5) ANDA patent challenge exclusivity –

²⁸ Both 505(b)(2) and 505(j) applicants must certify to each reference listed patents when they file their drug applications, stating either that: (1) under Paragraph I that such patent information has not been filed; or (2) under Paragraph II that such patent has expired; or (3) under Paragraph III the date on which such patent will expire, or (4) under Paragraph IV such patent is invalid or will not be infringed by the new drug. No ANDA or 505(b)(2) NDA will be approved by the FDA until all the listed Orange Book patents on the reference drug have expired, or have been successfully challenged by an applicant, or any applicable 30-month stay has expired. 21 C.F.R. 314.107; 21 U.S.C.A. § 355(j)(7)(A); 21 U.S.C.A. § 355(j)(2)(A)(vii); 21 U.S.C.A. § 355(j)(2)(A)(vii)(IV); *see also* H. REP. 98-857 (1984), *as reprinted in* 1984 U.S.C.C.A.N. 2647 at 2655 (“the committee recognizes that in some instances an applicant will have to make multiple certifications with respect to product or controlling use patents. For example, if the product patent has expired and a valid controlling use patent will not expire for three years, then the applicant must certify that one patent has expired and the other will expire in three years.”).

²⁹ These are often referred to as Paragraph I and II certifications. 21 U.S.C.A. § 355(j)(5)(B)(i)-(ii); 21 U.S.C.A. § 355(b)(2)(A)(i)-(ii).

³⁰ 21 U.S.C.A. § 355 (j)(5)(B)(iii).

³¹ 21 U.S.C.A. § 355(j)(2)(B).

³² 21 U.S.C.A. § 355(j)(5)(B)(iii).

180 days. The first four apply only to New Drug Application (“NDA”) filers. The fifth applies only to Abbreviated New Drug Application (“ANDA”), *i.e.* generic, filers. The Orange Book lists all exclusivities granted to each approved-drug product.

New chemical entity (NCE) exclusivity provides five years of exclusivity, from the date of approval of the first NDA, for new drug applications containing new chemical entities never previously approved by FDA, either alone, or in combination.³³ An NCE is a drug that contains “no active moiety previously approved by the FDA.”³⁴ No ANDA or 505(b)(2) application may be submitted during the five-year NCE period, except that such applications may be submitted after four years if they contain a certification of patent invalidity or non-infringement (*i.e.*, paragraph IV certifications).

NCE exclusivity is the only exclusivity that bars the FDA from even accepting applications for review (as opposed to allowing the submission and review of such applications and simply delaying FDA approval). The five-year exclusivity period does not bar the FDA from accepting another full competitor NDA if the sponsor of the second application has done all of the work itself. As a practical matter, NCE exclusivity delays competition for more than five (or four) years because, once the application has been submitted, it typically takes the FDA at least an additional year to review and approve the ANDA.

New clinical investigation (NCI) exclusivity grants three years of exclusivity for certain changes to a drug product.³⁵ It prohibits FDA from approving an application for the same product for three years.³⁶ This exclusivity begins at the approval of the product, and is limited to the changes in the product supported by the new clinical studies. To obtain NCI exclusivity, the application or supplement must contain reports of new clinical investigations conducted by the sponsor. Several requirements apply, including that the study be clinical (*i.e.*, in humans, not animals), that it be new (and generally not

³³ A “new chemical entity” or “NCE” is a drug that contains no active ingredient (including any ester or salt thereof) previously approved under section 505(b); 21 U.S.C.A. § 355, FD&C Act § 505 (c)(3)(D)(ii)-(iv), § 505(j)(5)(D)(ii)-(iv). The 5 year exclusivity provision of the Hatch-Waxman Act applies only to drug products approved under section 505(b) of the FD&C Act and not biologics. See FD&C Act. § 505(c)(3)(E)(ii).

³⁴ 21 C.F.R. § 314.08(a) (2008). An active moiety is “the molecule or ion, excluding those appended portions of the molecule that cause the drug to be an ester, salt (including a salt with hydrogen or coordination bonds), or other noncovalent derivative (such as a complex, chelate, or clathrate) of the molecule responsible for the physiological or pharmacological action of the drug substance.” *Id.* CDER makes NCE exclusivity determinations on all relevant applications. CDER reviews all relevant applications, with or without a request from the applicant, for an exclusivity determination. There is no requirement to apply.

³⁵ 21 C.F.R. § 314.108(b)(4)-(5).

³⁶ Unlike the five-year exclusivity for NCE, which bars submission of an application, the three-year exclusivity bars approval of an application, so that the agency can accept an application and review it during this time period. Like NCE exclusivity, new clinical investigation exclusivity will not bar approval of a full NDA where the applicant has done the work to support the same change for a drug product.

used for another drug approval purpose), and that it be essential to approval (*i.e.*, not merely interesting and useful).

Seven years of exclusivity also is available for Orphan drugs (*i.e.* drugs that treat a patient population with a target population less than 200,000).³⁷ The Orphan Drug Act of 1983 established an exclusivity period designed to provide an incentive to pharmaceutical manufacturers to develop drugs to treat rare diseases or conditions affecting relatively small numbers of persons. An orphan drug is defined as one treating a disease or condition which affects less than 200,000 persons in the United States or affects more than 200,000 persons but for which there is "no reasonable expectation that the cost of developing and making available in the United States a drug for such disease or condition will be recovered from sales in the United States of such drug."

Obtaining orphan drug status is a two-step process. First, the applicant must apply for, and receive, orphan-drug designation from the Office of Orphan Products Development at the FDA. Orphan designation qualifies the sponsor of the product for the tax credit and marketing incentives of the Act in exchange for developing the drug for a rare disease or condition. Second, like any other new drug, the orphan-designated drug must submit its full NDA for safety and efficacy review.

If the NDA is approved for the indication for which the orphan designation was granted, the developer of an orphan product receives seven years of market exclusivity following the approval of the product by the FDA. Orphan drug exclusivity protects the drug for the approved orphan indication against all other competitors. Unlike other exclusivities, orphan exclusivity protects the orphan drug even from a second full NDA for the same indication submitted by another applicant. Exclusivity applies only to the indication for which the drug has been designated and approved, however, so that a second application for the same drug for a different use could be approved by the FDA.

Any small molecule or biologic drug product can also obtain an additional six months of marketing exclusivity for demonstrating the safety, dosing and efficacy of the product in children.³⁸ Congress provided for a six-month pediatric exclusivity period in response to a perceived need for an incentive to encourage companies to complete and submit studies on the pediatric uses of drugs. Pediatric exclusivity attaches to all the applicant's formulations, dosage forms, and indications for products with existing marketing exclusivity or patent life that contains the same active moiety.

This is a broad grant because it attaches not only to the specific product that was studied in the pediatric population, but to all drug products (formulations, dosage forms, and indications) with the same active moiety. To balance this broad grant of exclusivity, the FDA requires pediatric studies of all drugs that contain the active moiety. This does

³⁷ 21 U.S.C.A. § 360aa-dd.

³⁸ 21 U.S.C.A. § 355a. The FDA grant of 6 months exclusivity is added to any existing marketing exclusivity or patent protection. This exclusivity incentivizes firms to conduct pediatric drug studies.

not mean that a sponsor must show that the drug is safe or effective in the pediatric population to obtain pediatric exclusivity. Instead, the goal simply is to develop a maximum amount of pediatric information as a result of the grant of exclusivity. Pediatric exclusivity may therefore be granted upon acceptance of the pediatric study reports.

Pediatric exclusivity is unique because it attaches to the end of all existing marketing exclusivity and patent periods. This distinguishes it from other types of exclusivity and patent periods, which run concurrently. For example, if a drug sponsor has five-year NCE exclusivity (which is valuable because it bars competitors from even submitting applications to the FDA); the six-month pediatric exclusivity will provide six additional months of NCE exclusivity. If the drug sponsor has three years of new clinical investigation exclusivity, which bars the FDA from approving a competing application, the six-month pediatric exclusivity will provide six additional months of the same protection. If the drug sponsor has a patent, FDA-enforced exclusivity will be added at the end of the patent term.

The Hatch-Waxman Act grants 180 days of marketing exclusivity to certain generic drug applications. The statute provides an incentive of 180 days of market exclusivity to the “first” generic applicant who challenges a listed patent by filing a paragraph IV certification and therefore runs the risk of having to defend a patent infringement suit. As a practical matter, if multiple ANDA filers file paragraph IV certifications on the same day and all are found acceptable for filing, multiple applicants may share the 180-day exclusivity. The statute provides that the first application to file a substantially complete ANDA containing a paragraph IV certification to a listed patent will be eligible for a 180-day period of exclusivity beginning either from the date it begins commercial marketing of the generic drug product, or from the date of a court decision finding the patent invalid, unenforceable or not infringed, whichever is first. These two events – first commercial marketing and a court decision favorable to the generic – are often called “triggering” events, because under the statute they can trigger the beginning of the 180-day exclusivity period. Approval of the ANDA alone has no effect on triggering the 180-day patent exclusivity period.

If there is no court decision, and the first applicant does not begin commercial marketing of the generic drug, there may be prolonged or indefinite delays in the beginning of the first applicant’s 180-day exclusivity period. Until an eligible ANDA applicant’s 180-day exclusivity period has expired, the FDA cannot approve subsequently submitted ANDAs for the same drug, even if the later ANDAs are otherwise ready for approval and the sponsors are willing to immediately begin marketing. Therefore, as a practical matter, an ANDA applicant who is eligible for exclusivity is often in the position to delay all generic competition for the branded drug.

In 2003, the Medicare Modernization Act amended the Hatch Waxman Act, to provide an 180-day market exclusivity period to the first generic company that seeks FDA approval to market a product prior to the expiration of certain patents relating to the branded drug product. No other generic manufacturer may obtain FDA approval to

market its product until the first generic applicant has sold its product for 180 days, unless the later generic applicant wins a patent challenge against the branded company.³⁹

The Hatch-Waxman Act also provides marketing exclusivity incentives to any NDA holder based on the level of innovation represented by the drug product. Any “new chemical entity” receives five years of marketing exclusivity. During this five-year period, the FDA may not review any 505(b)(2) or 505(j) applications that reference this new chemical entity. However, if an ANDA files a paragraph II certification against this NCE, exclusivity is limited to four years.⁴⁰ The FDA may not approve this application until after seven and one half years or patent litigation is resolved.⁴¹

³⁹ There are provisions for a generic company to forfeit the exclusivity period, which occur in limited circumstances.

⁴⁰ 21 U.S.C.A. §355(c)(3)(E)(iii); 21 U.S.C.A. §355(j)(5)(F)(iii).

⁴¹ 21 U.S.C.A. § 355(j)(5)(F).

APPENDIX C
PUBLIC COMMENTS
FTC ROUNDTABLE ON COMPETITION ISSUES INVOLVING
FOLLOW-ON BIOLOGIC DRUGS
NOVEMBER 21, 2008

NAME	TITLE OF COMMENT
American Association of Retired Persons (David P. Sloane)	12/22/2008
American Enterprise Institute (John E. Calfee)	12/10/2008 • <i>When Patents Are Not Enough: Data Exclusivity for Follow-On Biologics</i>
Amgen, Inc. (David W. Beier)	9/30/2008
Barr Pharmaceuticals, Inc. (Bruce L. Downey)	9/30/2008
Barr Pharmaceuticals, Inc. (Bruce L. Downey)	12/19/2008
Bayer HealthCare LLC (Sandra S. Oliver)	10/2/2008
Bernstein Research (Ronny Gal)	12/9/2008 • <i>Eight Thoughts on Biosimilars</i>
Biotechnology Industry Organization (John M. Taylor, III)	9/30/2008
Biotechnology Industry Organization (John M. Taylor, III)	12/22/2008
Biotechnology Industry Organization (Sandra J. P. Dennis)	2/24/2009

NAME	TITLE OF COMMENT
Biotechnology Industry Organization (Sandra J. P. Dennis)	2/24/2009 • <i>Unpatentable Drugs and the Standards of Patentability</i> , Benjamin N. Roin, (May 1, 2008)
Biotechnology Industry Organization (Sandra J. P. Dennis)	2/24/2009 • <i>Biosimilars, Data Exclusivity, and the Incentives for Innovation: A Critique of Kotlikoff's White Paper</i> , Henry C. Grabowski and Joseph DiMasi, (February 2009)
Biotechnology Industry Organization (Sandra J. P. Dennis)	2/24/2009 • <i>Data Exclusivity Period Length and Federal Government Savings from Enactment of the Biologics Price Competition and Innovation Act of 2007</i> , Joseph Golec, John A. Vernon, and Ted Buckley, (January 28, 2009)
Coalition for a Competitive Pharmaceutical Market (Annette Guarisco)	9/30/2008
CVS Caremark Corporation (David Golding)	12/22/2008
Duke University (Henry C. Grabowski)	12/22/2008
Duke University (Henry C. Grabowski)	12/23/2008 • <i>Data Exclusivity Periods for Biologics: Updating Prior Analyses and Responding to Critiques</i> , (December 22, 2008)
Duncan Bucknell Company (Duncan Bucknell)	1/9/2009
Eli Lilly and Company (Douglas K. Norman)	12/19/2008
Essential Action (Sarah Rimmington)	12/20/2008
Generic Pharmaceutical Association (Lisa K. Layman)	9/30/2008

NAME	TITLE OF COMMENT
Hospira, Inc.	5/19/2009
Hospira, Inc. (Lori N. Bowman)	9/30/2008
Hospira, Inc. (Lori N. Bowman)	12/22/2008
Johnson & Johnson, Inc.	3/17/2009 • <i>Executive Summary. Achieving the Right Balance between Innovation and Competition: The Role of Data Exclusivity</i>
Johnson & Johnson, Inc.	3/17/2009 • <i>Achieving the Right Balance between Innovation and Competition: The Role of Data Exclusivity</i>
Matrix Global Advisors, LLC (Alex M. Brill)	12/22/2008
Momenta Pharmaceuticals, Inc. (Bruce A. Leicher)	9/30/2008
Momenta Pharmaceuticals, Inc. (Bruce A. Leicher)	12/22/2008
Mylan, Inc. (David Rice)	1/5/2009
Novartis Corporation (Robert E. Pelzer)	9/29/2008
Novartis Corporation (Robert E. Pelzer)	12/22/2008
Office of Health Economics (Adrian Towse)	12/31/2008
Pharmaceutical Care Management Association (Missy Jenkins)	9/26/2008

NAME	TITLE OF COMMENT
Pharmaceutical Research and Manufacturers of America (Billy Tauzin)	9/30/2008
Pharmaceutical Research and Manufacturers of America (Billy Tauzin)	12/22/2008
Robert J. Reinhart	10/19/2008
Talecris Biotherapeutics (Bruce Bunyan)	9/30/2008
Teva Pharmaceuticals USA (David T. Sanders)	10/8/2008
Willkie Farr & Gallagher LLP on behalf of Hospira, Inc. (Kelsey I. Nix)	12/22/2008
Winston & Strawn LLP on behalf of Hospira, Inc (James F. Hurst,.)	12/22/2008
Wyeth (Matthew D. Eyles)	9/30/2008
Wyeth (Matthew D. Eyles)	12/18/2008
Zuckerman Spaeder LLP (William B. Schultz)	12/22/2008

Primary Source: <http://ftc.gov/os/comments/healthcarecompissues/index.shtml>

APPENDIX D:
PARTICIPANTS AT FTC ROUNDTABLE,
NOVEMBER 21, 2008

NAME	AFFILIATION
Alexis Ahlstrom	Avalere Health LLC
Geoffrey Allan	Insmmed Incorporated
Aaron F. Barkoff	McDonnell Boehnen Hulbert & Berghoff LLP
Rachel E. Behrman	U.S. Food and Drug Administration
Alex M. Brill	American Enterprise Institute; Buchanan, Ingersoll & Rooney PC
Steven B. Brugger	Momenta Pharmaceuticals, Inc.
Edward Buckley	Biotechnology Industry Organization
Kenneth J. Dow	Johnson & Johnson, Inc.
Suzanne B. Drennon	Federal Trade Commission
Christopher J. Garmon	Federal Trade Commission
David Golding	CVS Caremark Corporation
Ken Goldman	Novartis Corporation
Mark A. Goshko	Teva Pharmaceutical Industries Ltd.
Henry C. Grabowski	Duke University
Pamela Jones Harbour	Federal Trade Commission
Paul Heldman	Potomac Research Group
Linda R. Horton	Hogan & Hartson LLP

APPENDIX D

NAME	AFFILIATION
Elizabeth A. Jex	Federal Trade Commission
Esther M. Kleppinger	Wilson Sonsini Goodrich & Rosati PC
Jeffrey P. Kushan	Sidley Austin, LLP
John A. Lane	Hospira, Inc.
Bruce A. Leicher	Momenta Pharmaceuticals, Inc.
David A. Manspeizer	Wyeth
Suzanne T. Michel	Federal Trade Commission
Steven B. Miller	Express Scripts, Inc.
Douglas K. Norman	Eli Lilly and Company
Naomi Pearce	Hospira, Inc.
Audrey Phillips	Johnson & Johnson, Inc.
Hans Sauer	Biotechnology Industry Organization
William B. Schultz	Zuckerman Spaeder LLP
Rochelle K. Seide	Schwegman, Lundberg & Woessner PA
Christine J. Siwik	Rakoczy Molino Mazzochi Siwik LLP
Mateja Urlep	Novartis AG (Sandoz Ltd.)
Michael S. Wroblewski	Federal Trade Commission
Bryan C. Zielinski	Pfizer, Inc.

Primary Source: <http://ftc.gov/bc/workshops/hcbio/agenda/fobagenda.pdf>

Mr. PALLONE. Thank you very much. I always hate to stop anyone but we have time constraints. We are going to have a series of questions. I am going to start, and then we will go back and forth between Democrats and Republicans, as you know. First of all, I want to thank you for the report. As the expert agency charged with overseeing competition, as you mentioned, in the drug marketplace, the FTC's conclusions on how much exclusivity is needed to sustain innovation, I think is crucial to any resolution of many of the questions that have been raised on this issue. And I have to be honest to say that I, of course, hear mostly from people who have a financial stake in this, and I think it is essential that we have an objective assessment with regard to exclusivity, and that is one of the reasons why I think it is really crucial that you are here today and that this report came out.

Now members of the biotech industry argue that their patents are not as strong as those on traditional drugs, and are not strong enough to protect them from competition from follow-on biologics. If I understand you correctly, the FTC has reviewed all the evidence provided by the industry, as well as relevant patent law, and has concluded that the industry's claim is unsupported by the evidence. And this is an extremely important point because members of the biotech industry have premised their argument for a 12 to 14-year exclusivity period on the claim that their patents cannot fulfill the role they are supposed to. And it is important, I mean this is important enough that I want to be sure I understand your conclusions, and that there is no doubt about it.

So let me ask 3 questions. First, are patents on biotech drugs too narrow or too weak to protect them from competition from follow-on biologics? And, Mr. Wroblewski, obviously can answer as well.

Ms. HARBOUR. Yes. Mr. Wroblewski is the expert here, but I would say that our research has shown that the patents are strong in this area. In fact, as we look at the sector, the biotech sector, they have been very strong. The stocks in that area actually has been very strong and the general sector stock prices have gone down 30 percent, but in the biotech sector they have only gone down 15 percent. So we have not seen as much erosion in that area, and I do believe that the patents are strong in that area.

Mr. PALLONE. Maybe I will just go to the second question. The second question is will biotech patents provide less protection from follow-on biologics than the protection against generic competition offered by patents on traditional drugs?

Mr. WROBLEWSKI. The patent questions are really central to this entire debate. What we did was we examined—currently there is branded competition between competitors, and so what we did is we looked to see—we looked at all of those cases, which the industry gave us, and the ones that we found—all the cases that are out there doing our own research, and we broke them into 2 groups. The first group was the patents have been very strong. Both the drug molecule patents and the process patents have been very strong to keep other branded competitors off the market. When we looked at those cases in which the branded competitor or the pioneer had lost, the cases really turned on a factual determination that was central to that patent or how those claims were drafted.

It wasn't because the law prohibited them to draft their claims in a broader way.

And there are PTOs written, description guidelines, that say this is how you can—the legal requirements to get a broad patent to protect against those types of claims that FOBs are likely to make. The written guidelines allow the claims to be drafted broadly enough to protect against those types of patents. The one last thing we did is there was a great study that came out about a year ago that surveyed all of the patent cases in terms of has the law changed so that it is very difficult to get a broad scope on your patent to kind of guard against the potential threat of an FOB, and it found that the law had not changed and that the patent holders have the ability to draft their claims, to draft their patents to provide a potent shield against FOB competitors.

Mr. PALLONE. All right. Let me just ask my third question quickly. Is there any defect in the protection offered by biotech drug patents that justifies a longer exclusivity period than the period available to traditional drugs?

Mr. WROBLEWSKI. We found that there are no defects. There is an argument that there may be drugs that have been discovered but somehow are unpatentable because they are not novel any longer, and the requirement to get a patent is that a drug has to be novel. If that is the case, and we haven't seen any evidence that that is the case, then an exclusivity period similar to the way Hatch-Waxman had a 5-year exclusivity period for a new chemical entity that didn't have patent protection. Hatch-Waxman also gives 3 years for a new indication because that indication couldn't get patent. If there is something new that is being delivered that the patents won't incentivize, then it may be very appropriate to have an exclusivity period to encourage the companies to engage in the expensive R&D to test those drugs.

Ms. HARBOUR. Such as in the drugs for children population and the diseases that affect very small populations. That would be an example where one would offer an exclusivity period.

Mr. PALLONE. And not otherwise? But not otherwise?

Ms. HARBOUR. Unless there was an unpatentable drug as Mr. Wroblewski indicated.

Mr. PALLONE. OK. Thank you very much. Mr. Deal.

Mr. DEAL. First of all, let me make sure that I understand since there has been criticism about the scope of this hearing today, what I understand you to say is that your study and your testimony today is to deal with this question of competition and how it will evolve in a follow-on biologic marketplace, and questions like safety, interchangeability, those are issues that best address themselves to the Food and Drug Administration and not to you, am I correct?

Ms. HARBOUR. That is precisely correct.

Mr. DEAL. I didn't want you to be criticized for something you were not undertaking to do here today, and I think that is important because we all are concerned about safety. We are all concerned about the things that are within the province of the FDA. Let me focus in on what you have testified to, and what your report identifies. Most of us have heard from the lobbying community about how long should the period of exclusivity be. Now what I

hear and what I see at least in the summary that I have read of your report is that you don't even feel that there is even a need for any exclusivity period, and specifically I think your statement says the drug had already been incentivized through patent protections and market-based pricing, so you are saying that there are 2 protections that the pioneer drugs enjoy that is somewhat different from the chemical-based arena in these areas, one being that patents are strong enough.

And let me ask you specifically about that. As I understand you to say, the reason you think patents are stronger than we might be led to believe is that in this arena there are more and varied patents in the follow-on biologic arena than in the chemical arena, specifically including patents on manufacturing and the technology platforms on which they are based, is that correct?

Ms. HARBOUR. That is correct, and there is another component too that competition resembles brand to brand competition and in brand to brand competition the patents protect the innovation. In the follow-on context, you have the method of treatment patents. You have the product by process patents, the manufacturing process including the cell lines, so, yes, the report concludes that patents have been shown to be strong in this area.

Mr. DEAL. And the second component that gives protection that is more unique to this follow-on arena than chemicals is what you refer to as market-based pricing, and I think you have already told us that you do not expect the drastic reduction in pricing to occur on the pioneer product just because a follow-on comes on to the market.

Ms. HARBOUR. That is right.

Mr. DEAL. And that is an additional protection that the pioneer enjoys in this arena that they do not necessarily enjoy in the chemical arena?

Ms. HARBOUR. And the characteristics of this market is a follow-on, there would only be 2 to 3 follow-ons that would enter the market, and those follow-ons would only take 10 percent to 30 percent of the market share away, so the branded pioneer manufacturer would still enjoy 70 percent of its market share, and so there would be enough incentive and competition and pricing to satisfy the entrants contrasted with the generic market where after the first generic comes in taking 25 percent of the branded firm, then you would have 8 to 10 generics come in and then they would all cannibalize that 80 percent. So it is a very different competitive situation with the follow-on.

Mr. DEAL. Plus, also am I correct that the follow-on biologic will take a longer period of time for approval even with the exclusivity period even non-existent, it would still take longer to get a follow-on on the market than a traditional chemical-based generic would take?

Ms. HARBOUR. I am not sure about that. I am going to turn to Mr. Wroblewski. I think not, but I will let Mr. Wroblewski answer that.

Mr. WROBLEWSKI. The time to bring a follow-on to the market, the evidence shows would be about 8 to 10 years. The time it takes to bring a generic drug to the market is 3 to 5 years. The one thing about market-based pricing, the point that we were—to compliment

what Commissioner Harbour just talked about was that when you have a patent that allows you to charge, and you are the only one on the market and you have developed innovation, that allows you to charge a price, any price, a monopoly price, so if the period of time in which you enjoyed that monopoly is shortened the ability to raise the price, that is what marked-based pricing is all about to make up for that.

Ms. HARBOUR. Mr. Deal, I misunderstood what you had said. I thought you meant FDA approval, whether that would take longer, and my answer was, no, it would not. But, as Mr. Wroblewski said, yes, FOB drugs would take about 8 to 10 years to develop, and they would likely cost between \$100 million to \$250 million as compared to small molecule generic drugs, which would take 3 to 5 years to develop, and would cost roughly between \$1 million to \$5 million.

Mr. DEAL. Thank you.

Mr. PALLONE. Thank you, Mr. Deal. Chairman Waxman.

Mr. WAXMAN. Thank you very much, Mr. Chairman. Could you just repeat that last point? For biologic drugs it takes 8 to 10 years?

Ms. HARBOUR. Yes. Biologic drugs would take 8 to 10 years. Follow-on biologic drugs would take 8 to 10 years to develop, and it would likely cost between \$100 million to \$250 million, contrasted with the small molecule generic drugs where product development would take approximately 3 to 5 years to develop and would cost between \$1 million and \$5 million.

Mr. WAXMAN. So it costs more money.

Ms. HARBOUR. Yes.

Mr. WAXMAN. And it takes more time to develop these biologic drugs.

Ms. HARBOUR. Yes.

Mr. WAXMAN. And, therefore, they want to know they are going to have their full protection. Mr. Wroblewski.

Mr. WROBLEWSKI. I just want to make sure that we are talking about the follow-on and not the pioneer.

Mr. WAXMAN. Oh, I see. You are talking about the follow-on.

Mr. WROBLEWSKI. I just want to make sure.

Mr. WAXMAN. So if you got a new biologic drug, you got a patent and you think the patents are good, that is enough protection, we could give an exclusivity for that period of time. Patents, by the way, are for 20 years, isn't that right?

Mr. WROBLEWSKI. Correct.

Mr. WAXMAN. When we did the Hatch-Waxman Act, the patents were 17 years. We moved the patent period all the way to 20 now. And the Hatch-Waxman Act was a trade off. We said that we would allow generics to be approved through an abbreviated process in exchange for giving the brand name company additional time lost at FDA for the approval time. And that is called the patent term restoration. Well, we didn't know about biologic drugs in the mid-1980s, but these drugs get that patent term restoration, don't they?

Mr. WROBLEWSKI. Yes, they do.

Mr. WAXMAN. So they now have a longer patent time and they get the restoration period for the time spent at FDA. Your conclusion is pretty surprising because what you are saying is that if

somebody says they need 12 to 14 years of exclusivity, you don't think they need it because patents, and they have market-based pricing available under the current law, which you believe provides sufficient incentives for innovation.

Mr. WROBLEWSKI. It is not only that we believe it, it is what the industry has said for years that patents have been so essential to their development.

Mr. WAXMAN. Now you also concluded, and Mr. Deal pointed to this, so let us say we say at some period of time there is going to be an approval process for a generic follow-on, and that may take 8 to 10 years, so that is a long period of time once they even start to get the generic follow-on to come into competition. But once it is approved, it is not the same as a small molecule drug where people know it is the exact same drug and it could be substituted. A generic follow-on drug, which is going to take longer to get on the market, and they can't even be considered until the patent period is up or the exclusivity period is up, won't be substitutable. It is going to be like another brand name drug competing with a different brand name drug. What will that mean in terms of the loss of market to the generic competitor?

Mr. WROBLEWSKI. One of the aspects of branded drug competition is the substantial first mover advantage that the pioneer has, and so what is going to have to happen is when that follow-on comes on it is going to have to develop its own marketing and sales force to show that its product is actually more safe or more effective or somehow improves safety, convenience, efficacy for treatment of that drug to gain any market share. And that is actually a huge benefit for competition. Competition brings not only price competition, but it also brings improvements to the products which are very, very important, so you have to look at both of them.

Mr. WAXMAN. But the competition doesn't start immediately to drop that price because they have to convince the doctors and others that this is a follow-on that can serve the same purposes of the original drug.

Mr. WROBLEWSKI. That is correct, and when we have looked at market experience in Europe in which they have a bio-similar pathway in the 2 markets that we have looked at there are 2 drug markets. Both of them, after 3 to 4 years where the bio-similars have already been on the market only had about a 15 percent combined market total, so that means the pioneers still retain 85 percent of the market share which is totally different from the generic drug model.

Mr. WAXMAN. Will follow-ons provide—going to make high price biotech drugs more affordable and will these follow-ons provide other benefits to consumers?

Mr. WROBLEWSKI. I think the evidence that we have seen shows that they will come in at a 10 to 30 percent discount and a 10 to 30 percent discount on a drug that for a course of treatment annual is \$50,000 is a substantial savings, and it will then prompt the pioneer to then move forward to further refine and develop and improve its drugs which benefit consumers.

Mr. WAXMAN. So having an end point and then having competition even if it is not as strong as generics are for small molecule drugs does spur innovation?

Mr. WROBLEWSKI. Of course it does. Of course it does.

Mr. WAXMAN. Thank you. Thank you, Mr. Chairman.

Mr. PALLONE. Thank you, Mr. Chairman. Next, we have the gentlewoman from North Carolina, Ms. Myrick.

Ms. MYRICK. Thank you, Mr. Chairman. A couple of questions. This is just kind of a regional question relative to North Carolina. The biotech sector you know is very important in North Carolina and in how it plays into our economy. We see a total employment impact of over 200,000 jobs because of our rich biotech sector. No doubt a well-designed FOBs pathway could also generate additional economic growth. If the pathway were designed as the FTC describes, do you foresee any negative economic impact when it comes to profitability of innovative biotech companies?

Ms. HARBOUR. I don't believe that the report identifies any, and as I had said earlier the biotech sector is doing better than a lot of other sectors in today's economy looking at our stock industry.

Ms. MYRICK. Right. I heard you say that, so you just don't think that there is any—the other thing I wanted to ask was about the European Union. You know their system is different than ours is, and when you look at the policies that we have and they have, do you think that their policies generally translate to the United States because we have such a glut of biotech companies here and our existing patent system the way it is set up?

Mr. WROBLEWSKI. The 2 things that we look at in terms of the European market, they do things a little bit differently in terms of their patent coverage, and they do things differently in determining at the European level, they decide what is safe and effective for a bio-similar and they are leaving to the states, the members states and the countries, to decide what would be interchangeable. That is a slightly different structure than we have here in the United States. But the commercial aspects in terms of what these large multi-national companies are doing can provide some insight—in Europe can provide some insights into what they are likely to do here in the U.S.

Ms. MYRICK. One more question. When you talk about the delay in the time it takes for the price differential between the FOBs and the innovative biologics, it becomes significant because the point of entry for these products is different than traditional generic drugs. The study says that the price differential would be 10 to 30 percent of the original therapy's price. Do you think that that would put pressure on the insurers in large companies, pressure on providers to make the time period shorter?

Mr. WROBLEWSKI. To make the time period shorter?

Ms. MYRICK. Yes, of bringing them to market. You don't think there is a possibility that can even happen from what you said basically?

Mr. WROBLEWSKI. Right.

Ms. MYRICK. I think that is all at this point, Mr. Chairman. Thank you.

Mr. PALLONE. Thank you. Let me mention to everyone that we will have 2 votes. One has already been called, but I would like to get at least 2 more of our members to ask questions before we go. So next is the gentlewoman from Wisconsin, Ms. Baldwin.

Ms. BALDWIN. Thank you. Commissioner, the FTC report claims that the development time for small molecule and biological drugs are roughly equivalent, and I would like to highlight the example of Flugen, which is a company that I talked about during my opening remarks. They are currently working on an adjuvant to the standard flu vaccine which would allow 10 times as many doses from the same stock of vaccine, so basically allows what would be usually 1 dose to be used for more vaccines. This adjuvant was patented from the University of Wisconsin-Madison research lab in the year 2001, but will likely not make it to clinical trials until the year 2011, and then it is predicted to be another 7 years to get to market, which leaves only 3 years of patent protection. And so I am wondering how do companies like this factor into your analysis? Do you think the patent protections are sufficient in an instance like this?

Ms. HARBOUR. Could I just clarify the first part of your question? I believe you said something was equivalent. Would you just go back to that, please?

Ms. BALDWIN. Absolutely. My understanding is that the FTC report claims that the development time for small molecule and biologic drugs are roughly equivalent.

Ms. HARBOUR. They are not.

Ms. BALDWIN. OK. Maybe you could shine some light on—

Mr. WROBLEWSKI. There are 2 things that we are talking about. One is if you are looking at a pioneer drug, the first in class, the innovator, if you look at a biologic drug or a chemical drug, they roughly cost the same amount to develop and it takes the same amount of time. If you then look at the follow-ons or the generics, the generic is much quicker to come to the market than a follow-on. Does that make sense? So the pioneers are equivalent. The second in the class, so to speak, take a little bit longer for follow-ons.

Your question is whether the patent restoration that—the example that you gave is basically they are only going to have 3 years left or 4 years left on their patent. They get patent restoration now so they would be able to add back that time that was lost in FDA approval. That applies to them now. And if that isn't sufficient because of the long period of—the longer period, so to speak, of testing for FDA approval then the fix would be to fix the restoration of the patent, not to then add an additional layer somewhere else, but to fix the underlying problem, which is what the patent isn't providing the length of time that was caught up in the FDA approval process.

Ms. BALDWIN. Let me also ask you a little bit about changes in technology that take place over these periods of time. Over the lifetime of a patent for biologics manufacturing technology will surely improve making it much easier for companies delivering biosimilars to enter the market. These companies will gain really at the innovators significant expense. And isn't that an argument for some period of exclusivity to be sure that innovators will still be willing to take the up front risks to develop these incredible medicines?

Mr. WROBLEWSKI. You know, those technologies that they are going to be developing actually would be applicable to the pioneer as well, so the pioneer actually can benefit from the increase in

technological advancement. For example, if a follow-on develops a better manufacturing process, that manufacturing process can be then imported or be used by the pioneer as well, and so that competition to improve innovation benefits not only follow-on but can benefit the pioneer as well.

Mr. PALLONE. OK. Mr. Murphy. I am sorry. Mr. Buyer.

Mr. BUYER. Thank you very much.

Mr. PALLONE. Before you start, let me just mention he will be the last speaker before we break for the votes, and then we will come back right after.

Mr. BUYER. I would like to know who asked you to do this report. Who asked you to do this report?

Ms. HARBOUR. Thank you for that question. Before I answer that, there is a lot of commonality in this room although it may not—

Mr. BUYER. That is not answering my question. Answer my question.

Ms. HARBOUR. I did.

Mr. BUYER. Were you contacted or encouraged by any member of the House and Senate or staff—

Ms. HARBOUR. May I answer your question, sir?

Mr. BUYER. Yes.

Ms. HARBOUR. In 2003, I read the Commission's IP report. I was a new commissioner. I read it, and there was a footnote that talked about generic biologics they called it then and how there was a great debate and a lot of controversy about this issue and how it was keeping potentially life-saving drug products from the American consumer. So as a commissioner, I went to my staff and I said this is an issue that is very important to the American people. And I know that my staff is very expert in these areas. I said can we take a look at this and see if we can add to the debate. That is how this issue came to the fore.

Mr. BUYER. So you did this on your own?

Ms. HARBOUR. No. It was with the approval of the other commissioners, but I did see this issue back in 2004.

Mr. BUYER. Do you see yourself as an expert in promoting competition in U.S. markets?

Ms. HARBOUR. No, I do not. No. I see myself as an expert on the American consumer and trying to be a champion of the American consumer much as most of Congress is.

Mr. BUYER. Since you are eager to sit at the table and discuss health, would you be equally as eager to turn to your commissioners and ask that the FTC consider studying the effects of the proposed public health plan options on competition in the health insurance market?

Ms. HARBOUR. First of all, I was summoned to the table. I am not eager to sit here, but I am happy to sit here.

Mr. BUYER. I am going to just ask you to answer the question that I have asked.

Ms. HARBOUR. Would you repeat it, please?

Mr. BUYER. Would the FTC consider studying the effects of the proposed public health plan options on the competition in our health insurance market?

Ms. HARBOUR. If we are directed to study anything by Congress—

Mr. BUYER. Well, you weren't directed to do this study and give it to us. You did this on your initiative you said with pride.

Ms. HARBOUR. Yes, and we do a lot of things on our own initiative at the Federal Trade Commission.

Mr. BUYER. Would you on your own initiative consider the public option plan discussed by the President and its impact on competition in the insurance market?

Ms. HARBOUR. If we were asked to do so we—

Mr. BUYER. You are asked to do so. All right? I ask you to do so.

Ms. HARBOUR. But we would have to vote on that and it would have to be decided by a majority of the Commission.

Mr. BUYER. Right. OK. Oh, wonderful. I will even put it in writing to you. I will ask you to do that, and then you can consider with the other commissioners. Would that be OK?

Ms. HARBOUR. Sir, you may do whatever you like and we will—

Mr. BUYER. Well, you have just done whatever you like, right, on your own initiative. Let me just do this. If you are willing to—now you are willing to consider the public plan options in the insurance markets impact on competition because you are so concerned about the consumer. Number 2, I am going to ask you for another report. Here in the House, we just passed a tobacco bill. The Senate is about to pass a tobacco bill that locks down the tobacco market, as a matter of fact, almost eliminates competition because we don't even have harm reduction anymore, and so I am going to ask for a second report for you also to consider, the impact of tobacco legislation and competition in the marketplace. I am going to ask you for 2 reports, OK?

Now the other question I have is I noted in a footnote that you had sent a letter to Chairman Pallone outlining preliminary views on the likely effects of the regulatory approval pathway. That is great. That wasn't shared with any of us. If this had been done back in May of 2008, this is a hearing, Mr. Chairman, that should have happened some time ago, so I appeal to you that this not be our only hearing that we have—

Ms. HARBOUR. Sir, I believe that letter is on the public—

Mr. BUYER. Ma'am, I am not asking any question of you.

Ms. HARBOUR. It is in the public record.

Mr. BUYER. Ma'am, I am not asking any question of you.

Mr. PALLONE. If you are asking me the question—

Ms. HARBOUR. The letter is on the public record.

Mr. PALLONE. Let me just cover it. Is the gentleman yielding to me?

Mr. BUYER. My point is, this is my personal opinion, this is a hearing that we should have had later—at an earlier time, not now, and so my appeal to you is, Mr. Chairman, that we bring the FDA in so we can look at—

Ms. HARBOUR. And CC'ed.

Mr. BUYER. Pardon?

Mr. PALLONE. Wait a minute. Let us please—

Mr. BUYER. Ma'am, I am not asking you any question.

Mr. PALLONE. Mr. Buyer, look, it is a little unclear who you are asking the question of. It may not be obvious to you but it is in-

creasingly to the 2 of us that we are not sure. The question is to me at this point?

Mr. BUYER. All right. My appeal is that you bring the FDA in so we can get into the efficacy and safety issues. That is my appeal to you.

Mr. PALLONE. OK.

Mr. BUYER. So I am not asking any questions of this witness.

Mr. PALLONE. Let me just—if you would yield. Well, we are out of time anyway. But let me answer the question. First of all, the letter you mentioned, it is my understanding that that letter was posted on the web site for the committee and circulated almost a year ago, the one that you mentioned that was sent to me. And as far as the second question, I have already stated that we are going to have additional hearings and this is just the first one so I just want to make that clear again.

Mr. BUYER. All right. I have a unanimous consent request.

Mr. PALLONE. You have a unanimous consent request?

Mr. BUYER. Yes.

Mr. PALLONE. Go ahead.

Mr. BUYER. I have a letter from the Association of American Universities, which includes the leading research universities, not only researchers in Indiana and Purdue, but over 60 in the country, and I would ask unanimous consent that the Association of American Universities letter be inserted into the record. Obviously, they are seeking providing 12 years of data exclusivity, and I don't believe it is very clear from the FTC report that they include the nation's leading academic researchers and what their opinions are.

Mr. PALLONE. Without objection, so ordered.

[The information appears at the conclusion of the hearing.]

Mr. PALLONE. And the committee is going to now recess until we have the conclusion of these 2 votes and then we will come right back. Thank you.

[Recess.]

Mr. PALLONE. The subcommittee will reconvene. Thank you for still being here. And we go to the gentlewoman from the Virgin Islands, Mrs. Christensen.

Mrs. CHRISTENSEN. Thank you, Mr. Chairman, and again thank you for holding this hearing and welcome to the commissioner, Commissioner Harbour. The report makes several statements to support its conclusion that a 12 to 14 data exclusivity period is unnecessary. One statement is that there is no evidence that patents claiming a biologic drug product have been designed around more frequently than those claiming small molecules. And the other is that because there is no evidence about the lack of patentability of new biologic products nor that market forces have been insufficient to incentivize development the Commission has not recommended a specific length for exclusivity period. If there are no bio-similar pathways that exist, how could there be any evidence as to how patents could be worked around? Isn't the whole point that in a bio-similar world patentability changes because the approval standard has been reduced from sameness to similarity?

Ms. HARBOUR. Let me just say that in this market we know that the follow-on biologic will resemble brand to brand competition. And we know that the patents are strong on biologic drugs. Now

your question was rather long, so I didn't get all of it but I am going to let Mr. Wroblewski answer what he heard, and then I will come back.

Mr. WROBLEWSKI. OK. Sure. Your question was to the extent that if there is no follow-on biologic how can there be—if there is no pathway yet how can there be any evidence. What we looked at is the existing brand competition because these markets are very large, and so there is plenty of opportunity for another branded competitor to come into the market, duplicate all the clinical and safety efficacy data, get a full new drug, and then compete, but we found that the patents have been so strong in so many of these markets that it has even kept out a branded competitor from doing just that.

Mrs. CHRISTENSEN. So from creating a similar product that comes through a different pathway?

Mr. WROBLEWSKI. If you create the similar product what you are doing is you are saying to the FOB you don't have to do as much clinical testing but you are still going to have to do some in order to be approved and you can rely on the FDA's previous findings about the innovator drug that it is safe and effective and you won't have to do as much. But if the patents have been strong to keep out the branded competitors they are going to be equally as strong to keep out the follow-on competitors who have to be similar.

Mrs. CHRISTENSEN. I guess you don't really make a recommendation as to what the period of exclusivity is, but just given the trends and the complexity of the drugs, and all of the other factors, the length of time that the very specific processes that have to take place that may not be able to be duplicated, the amount of investment that has to be made, can you just explain to me again why we would not provide for a longer period. It just seems, I mean as a physician I know that I would have a lot of difficulty. I would have to adjust myself to generics period to begin with because my patients, some of them wouldn't accept them even if I did. But because there may be immune differences in how a person reacts immunologically and the medication, why wouldn't you give these complex molecules with all the other factors a longer period of exclusivity?

Ms. HARBOUR. Let me take a stab at that. We feel that the patent protection and market-based pricing is enough. Why? First of all, the rationale for 12 to 14-year branded exclusivity period basically would be to compensate for any perceived failures of the patent system to reward and protect and to incentivize biologic drug innovation, but our report has not found any perceived failure. Therefore, we found that branded exclusivity was not necessary because the branded biologic manufacturers are likely to enter the market and earn substantial revenues even after follow-on entry.

And the follow-on biologics are unlikely when they do enter the market against the pioneer manufacturers, they are unlikely to price discount more than 10 to 30 percent. That means that the branded pioneer manufacturers are likely to maintain their advantage. They will still retain 70 to 90 percent of their market share after the follow-on biologic enters. They are still making very excellent profits and the biologic product has already, as I said, been incentivized through patent protection and market-based pricing.

Mrs. CHRISTENSEN. Well, my time is up. If there is another round, I may come back.

Mr. PALLONE. Just to know, we are not going to have another round but thank you, Mr. Murphy.

Mr. MURPHY OF PENNSYLVANIA. Thank you, Mr. Chairman. Some quick questions here. The comment that you just made about 70 to 90 percent, they will maintain 70 to 90 percent of their market share, and they will likely continue to reap substantial profits. What is the basis of that statement? Likely, what does likely mean?

Mr. WROBLEWSKI. The basis of the statement is the experience that we have seen so far in Europe in terms of how they have priced and then with the limited experience that we have seen with the one example with Humatrope here in the U.S. It is a biologic drug but happens to be approved under the Federal Food, Drug, and Cosmetic Act so it is an exception. So when we looked at those, but then it is also based on the Commission conducted a workshop in which we had the biotech industry. We had the potential FOB competitors. We had the payors, the PBMs, and the——

Mr. MURPHY OF PENNSYLVANIA. Did you have the companies that actually do the research and development in the room? Did you have the companies that actually developed the new drugs in the room?

Mr. WROBLEWSKI. Oh, yes. Oh, yes.

Mr. MURPHY OF PENNSYLVANIA. And did they say that they thought it was maintaining at 70 percent——

Mr. WROBLEWSKI. Yes.

Mr. MURPHY OF PENNSYLVANIA. Did they say maintaining 70 percent market share they could continue to——

Mr. PALLONE. I couldn't even hear some of the comments you made. I don't know if the reporter could. Maybe don't repeat it now but just stay close to that mike.

Mr. WROBLEWSKI. OK. I am almost swallowing it.

Mr. MURPHY OF PENNSYLVANIA. I understand that nearly 90 percent of biotech companies have remained unprofitable. In 2008, a third of them had less than 6 months cash on hand. They have to go out and get venture capital for these things, and if we say to the venture capitalists who are investing that we are going to reduce that by several years of return on investment here that to have someone come through—I wasn't in this room when everybody met. Let us take out the payors. Let us take out the FOBs who is going to benefit from this. Just the companies, they said, yes, it is fine with us, cut us down to 5 years and we can make do with this?

Mr. WROBLEWSKI. No. No.

Mr. MURPHY OF PENNSYLVANIA. OK. What did they agree to?

Mr. WROBLEWSKI. They agreed to what the market effect would be of FOB entry.

Mr. MURPHY OF PENNSYLVANIA. They are fine with it?

Mr. WROBLEWSKI. It was their research that——

Mr. MURPHY OF PENNSYLVANIA. Down to what level, down to how many years exclusivity?

Mr. WROBLEWSKI. Say that again.

Mr. MURPHY OF PENNSYLVANIA. Down to how many years of exclusivity are they fine with?

Mr. WROBLEWSKI. What we were trying to do was analyze how competition was likely to develop.

Mr. MURPHY OF PENNSYLVANIA. But down to how many years exclusivity, did they comment on that?

Mr. WROBLEWSKI. They have strenuously advocated for a 12 to 14-year period of exclusivity.

Mr. MURPHY OF PENNSYLVANIA. So they are OK if it stays 12 to 14 years and to have competition into the market there, is that what they said, they can still—

Mr. WROBLEWSKI. Say the last piece again. And the—

Mr. MURPHY OF PENNSYLVANIA. The 70 to 90 percent of their market share but it is at 70 to 90 percent of their market share so let FOBs come in, but would that also still maintain some exclusivity for that 12 to 14 years?

Mr. WROBLEWSKI. What we had tried to do was to see how the competition was likely to develop to determine whether—

Mr. MURPHY OF PENNSYLVANIA. I only have 2 minutes left. I just need an answer. Does that—are they agreeing, yes, we are OK with competition if we can keep the 12 to 14-year exclusivity, and that allows us to raise enough money in an unprofitable time to do research on new drugs?

Mr. WROBLEWSKI. I don't think they ever agreed that they would be able to keep 70 to 90 percent. It is just what the experience has shown that they would—

Mr. MURPHY OF PENNSYLVANIA. Well, I am confused because I thought you said that they all met together and they told you they were supportive.

Mr. WROBLEWSKI. Everybody predicts that the effect of a follow-on biologic will be—that they will come in at a 10 to 30 percent discount, and if they do that the brand or the pioneer is likely to retain 70 to 90 percent of its market share.

Mr. MURPHY OF PENNSYLVANIA. OK, but I thought you said—

Mr. WROBLEWSKI. We looked at what that implication was.

Mr. MURPHY OF PENNSYLVANIA. I need an answer here. I am really not trying to be funny, but I don't want to dance around this because I want to make sure we have plenty of money to continue to develop life-saving drugs. That is what I want. Cheap drugs that don't cure anything are worthless. Expensive drugs that no one can afford are worthless. So I need to know. You talked about some people sat around and they agreed to something. What the heck did they agree to, and if they didn't, don't tell me they did. Are they saying that this 12 to 14-year exclusivity remains, are they saying they are OK with competition, are they saying they are OK with making it 5-year exclusivity? What specifically did they say in 3 words or less? I just need an answer quickly.

Mr. WROBLEWSKI. They agreed that competition would be like a branded competitor and we have ways to deal with branded competitors now.

Mr. MURPHY OF PENNSYLVANIA. Did they comment at all on the years of exclusivity or is your report not touching on today?

Mr. WROBLEWSKI. No. It describes completely that they have put forth a model that shows that they need 12 to 14 years.

Mr. MURPHY OF PENNSYLVANIA. OK. One other thing I want to ask real quick. The issue of similarity so a molecule may change

its large molecule. A molecule may change. We are not going to require the FDA to do testing on those?

Mr. WROBLEWSKI. We took it as a given that the FDA would approve a safe and effective product, whatever that required.

Mr. MURPHY OF PENNSYLVANIA. So the FDA may still require additional testing of some of these drugs?

Mr. WROBLEWSKI. And that is the reason why it is going to be so expensive to bring in an FOB.

Mr. MURPHY OF PENNSYLVANIA. OK. So just changing a molecule on something, I mean you could change one molecule in an H2O formula and make something that is toxic versus something that is necessary so I hope that that is an important part of this whole report. If that is something we have discussed more perhaps you can elaborate on this for me because it is something you made reference to in writing and also in your testimony here. I really would like to know what that means because that is going to be very important to understand how we can have a competitive marketplace and also make sure there is sufficient funding in here that we can keep moving forward in developing these new drugs. I would be grateful for that. The procedure will be to let the chairman know and we will go on from there. Thank you so much.

Mr. PALLONE. Let me mention to you and to the members, and obviously as always you will be able to pose questions in writing that we would ask you to respond to after the hearing. The gentleman from California, Ms. Eshoo.

Ms. ESHOO. Thank you, Mr. Chairman. The first thing I would like to start out with is to ask for unanimous consent to place in the record the comprehensive responses to every question raised by the subcommittee from the chief scientist of the FDA, Dr. Frank Torti, which was peer reviewed, and, second, the exhaustive economic analysis of data exclusivity of biologics by Henry Grabowski, whose name has been mentioned several times by several members on both sides of the aisle today. He is the director of the Program of Pharmaceuticals and Health Economics at Duke University. So I would ask that these be placed in the record.

Mr. PALLONE. Let me just ask, these are the comments by the FDA under the Bush Administration, is that what they are?

Ms. ESHOO. Well, the FDA is the FDA regardless of what Administration it is under.

Mr. PALLONE. No, no, I just want to make sure because I know we have asked—I am only asking because I know that we have asked the FDA, the current FDA, too, but these are the ones from the previous, right? Let me see them.

Ms. ESHOO. You know what, Mr. Chairman, I think you know what I asked. I am just asking for unanimous consent to place this in the record. If people want to read it, they will have access to it. If they think it is garbage, they can throw it out. It doesn't force anyone. It is a very simple request.

Mr. PALLONE. No, no, I agree. I am just trying to verify what it is.

Ms. ESHOO. Read it and then you will see. Is there unanimous consent to it?

Mr. PALLONE. Well, normally I like to know what it is before I agree.

Ms. ESHOO. I just read it into the record.

Mr. PALLONE. Tell me again. It is the FDA—

Ms. ESHOO. These are the comprehensive responses to the questions that the members of the subcommittee almost 2 years ago before we had the meeting—

Mr. PALLONE. Right, but we have also asked them—these are the ones from the previous Administration. We have asked them again in the current Administration.

Ms. ESHOO. You don't agree with what the FDA responded, but I still would like that in the record.

Mr. PALLONE. No, I just want to make sure that they are the ones from the previous Administration. That is what we are talking about, right?

Ms. ESHOO. What is the date on it? It is September 18, 2008.

Mr. PALLONE. OK.

Ms. ESHOO. So it is just before my candidate for President won.

Mr. PALLONE. All right. So ordered.

[The information appears at the conclusion of the hearing.]

Ms. ESHOO. In trying to read the report, digest it, and then analyze it in the unfair time frame that was established either by the FTC or by the committee, I don't know which it is, there is something that stood out to me, and that is throughout the report, throughout your report you base the—you talk about obviously the generics that are the result of Hatch-Waxman, which we all celebrate, and this new attempt to use that framework, very broad framework, and apply it to biologics. But what you, I think, fail to state and then develop in the report is that under Hatch-Waxman the compounds, the pharmaceuticals must be identical. That is by law. Biologics, bio-similars, think of the 2 parts of that word, will be similar. They cannot be identical. I don't know what scientists you brought in to instruct you on this, but I have to say that to base your report, as I read it, I think it is deeply flawed because you base your outcome and your analysis of bio-similars on the previous regimen and the previous law, which is very different.

I don't see where you have taken into consideration the differences between the two which is what makes this case very complex. We have a regulatory framework today in which any new biologic will receive, and I want to move on, because I want to ask my questions but that is an observation, any new biologic would receive 20 years of patent protection and no potential for bio-similar competition. Innovators and investors are assured that as long as their patents are in force, there is no possibility of a competitor going to the FDA using the innovator's safety and efficacy record and taking a shortcut to the market to compete against them.

Now we are proposing to move to a policy in which patents will remain in force but competitors will be able to come to market to compete against an innovative product without going through a full-blown FDA review. As you point out in the report, this will cost a bio-similar manufacturer about a tenth of the cost for an innovator or a non bio-similar competitor to bring a product to market. Now how can this not possibly change? How can this—because you say in your report that investment incentives won't change. How can this not possibly change the investment incentives in bio-technology? If a venture capitalist or a drug company is contemplating

a new product for development, won't this fundamentally alter their rise/reward calculation? This has to have an examination. I don't know where you leap frog to. It is almost as if this doesn't exist or that if we don't talk about, we don't have to deal with it, therefore, it doesn't exist.

So I think you need to answer that. And I want to bring out my next question as well. Your report states that a 12 to 14-year exclusivity period, this is quote, "is unnecessary to promote innovation by pioneer biologic manufacturers." This position is based on your assumptions that patent workarounds will be no easier to accomplish for biologics than they have been for small molecule generic drugs. You also state that data exclusivity is only justified for products that are unpatentable, but I see no substantiation at all for these positions in your report. That is why I question whether past or present information about small molecule generics is a reliable predictor for biologics, and that is why I question the basis for your assumptions.

We have absolutely no experience, and I want to repeat that. We have absolutely no experience with the similarity standard that will be used for biologics for the approval of bio-similars, so how can you be sure that a new and untested standard would not facilitate a path for patent workarounds for biologics? How can you be sure that the different nature of biologic patents in conjunction with the similarity standard would not facilitate patent workarounds? How can you be sure? And, you know what, guessing in this is not going to be good enough. I would challenge you to ingest what comes out without the kind of scrutiny of the FDA and comparing one with the other as if they are the same as if it is apples and pears. It is not. How can you be sure that today's science and the scientific advances in the future would not make it easier for bio-similar companies to work around biologic patent claims?

I think that this is a real chink in the armor of the report or just in the report, which I have to tell you at quarter to 1:00 this morning, I thought really suggested a lot of guesswork on the part of the FTC. And let me hold something up, and I don't know if you had anyone come in and show you this. This is a regular drug, small molecule compound. This is tamoxifen. Look at it. It is all the same. This is herceptin. This is herceptin. This is herceptin. If this picture doesn't speak a thousand words where you use the model throughout your report based on the generics of the small molecules and apply it to this, I want to tell you something, patients are going to be in big trouble in this country. Patients are going to be in big trouble in this country.

And if efficacy of this movement is not taken into consideration, God help us. Now there is something else that has gone around in the committee for those that are opposed to my viewpoint, and they have every right to oppose it. But I want to—and there are other members that have touched on this. We cannot take for granted those that innovate to pursue the cure of these deadly diseases. The FDA is not going to do it, the Energy and Commerce Committee is not going to do it. We have a private sector that does it. Yes, there need to be new rules of the road because we want lower costs and safe products. But that role cannot be diminished, and, I don't know, I looked at the back of your report. Did you have any

people that do the investing in this come and be part of your round table? If they were law firms, I didn't recognize them.

Mr. PALLONE. Let me just—we are like twice the time so I am just going to ask you to—I know you can't respond to everything but—

Ms. ESHOO. Well, there was an assertion, Mr. Chairman.

Mr. PALLONE. But if you could just respond as quickly as you can because we need to move on.

Ms. HARBOUR. I will. There were just a number of assumptions. First of all, let me just apologize to you for the lack of time you had to read the report.

Ms. ESHOO. Well, why did that happen to begin with? Were you told—how long have you been working on this?

Ms. HARBOUR. The commissioners received the report at 4:00 on Tuesday evening.

Ms. ESHOO. No, no. How long has the FTC been working on this report?

Mr. WROBLEWSKI. We announced our workshop because we had a public hearing in August of last year.

Ms. ESHOO. How long have you been working on it?

Mr. WROBLEWSKI. Ten months.

Ms. ESHOO. Ten months.

Ms. HARBOUR. And it was finished on Tuesday.

Ms. ESHOO. And you notified the committee that it was complete when?

Mr. WROBLEWSKI. I notified the—the beginning of last week that it would be ready.

Ms. HARBOUR. And it was ready Tuesday at 4:00.

Ms. ESHOO. And did the FTC—was it the FTC that refused to put the report out to members and only after cajoling that we finally got it and that some of us took it home to read last night?

Ms. HARBOUR. Let me be really clear. The report was finished Tuesday at 4:00 p.m. The commissioners of the Federal Trade Commission voted this Tuesday, this week, at 4:00 p.m. on the report. There were embargoed copies that went probably before we even voted on it, but it went to the full committee the very next day.

Ms. ESHOO. You know what, let us get to the—

Mr. PALLONE. All right, but we have to move on.

Ms. ESHOO. I would like you to answer the questions that I posed.

Ms. HARBOUR. OK. There was an assumption that was made, you said that the report applied the Hatch-Waxman framework in this context. It doesn't—

Ms. ESHOO. Similarities. I am sorry. The identical standard and use it and apply it to the similar standard.

Ms. HARBOUR. The report actually did not say that. In fact, the approval pathway for biologics will be very different than the Hatch-Waxman approval process, and that is why I started by apologizing that you didn't get a chance to read the full report because it doesn't say that the approval process is similar. It is not. In fact, we are advocating that a Hatch-Waxman approval process would not be appropriate in the case of follow-on biologics. And the reason we say that is because it mimics brand-to-brand competition.

Ms. ESHOO. I am not talking about the approval process. I am talking about the investment incentive. You all are the ones that are in charge of competition. That is why, I guess, you got involved in this whole issue and that is why I think——

Mr. PALLONE. If you would just answer that, and then we have to move on. I am just going to have to move to the next person.

Mr. WROBLEWSKI. What we did is we looked at—we did look at the investment incentives for the biologics and compared them to the investment incentives for a small molecule drug, the Hatch-Waxman type drug, and the research that we have that is out there, and I provided to your staff earlier, was that the actual time and the cost to develop a pioneer biologic drug versus a pioneer small molecule drug are the same.

Mr. PALLONE. All right. I have to go. Mrs. Capps is the next for questions.

Mrs. CAPPS. Thank you. Thank you, Honorable Commissioner, for being here for this long. One of the reasons, I have 3 different questions to ask, one of the reasons that has been given for a 12 to 14-year exclusivity period is that without such a lengthy period start-up biotech companies will not be able to interest venture capitalists in investing in their companies, and without venture capital these companies cannot survive. Some believe that this specific number of years is very difficult to evaluate. Before Congress makes a determination on exclusivity periods, this hearing is because we feel a duty to determine whether there is adequate evidence to support arguments in its favor. First question, did the evidence gathered by the FTC in the course of its investigation support the claims that venture capitalists will no longer invest in start-up biotech companies without this 12 to 14 years of exclusivity?

Mr. WROBLEWSKI. We believe that patent protection will still provide those incentives. Patent protection plus market-based pricing will still provide those incentives for venture capitalists to invest in start-up biotech ventures.

Mrs. CAPPS. I know you have mentioned this already. I just wanted to get it clearer from my perspective as well. Next question, is there evidence that start-up biotech companies will still be able to recruit venture capital in during like a 5-year period comparable to what the traditional drugs have or the small molecule drugs have?

Mr. WROBLEWSKI. Yes, because patent rights are still going to be strong.

Mrs. CAPPS. Do you have evidence that this is the case?

Ms. HARBOUR. Well, we have seen if you take a look at the stock market in the biotech market the stock prices only went down 15 percent compared with the general market indices went down 30 percent.

Mrs. CAPPS. But you are using that as one method of your valuation?

Ms. HARBOUR. There are probably more as well, but that is what comes to mind.

Mrs. CAPPS. Are there others?

Mr. WROBLEWSKI. The only thing I was going to add was the venture capital that has come into the biotech industry in the past quarter has actually been very robust.

Mrs. CAPPS. And right now there is no 12 to 14-year exclusivity because that is what we are debating, so right now they have nothing—pardon?

Mr. WROBLEWSKI. That is true, there is no 12 to 14-year exclusivity.

Mrs. CAPPS. There is the same as small molecule. Finally, another kind of tact, the FTC report concludes, as you just mentioned, that 12 to 14 years of exclusivity is unnecessary because patents and market-based pricing available under current law provides sufficient incentives for innovation. I am particularly interested in one of your conclusions that given an excessive period of exclusivity may in itself have negative consequences, and that may actually harm patients. This is a piece that I would like you to spell out. What are some of these negative consequences, particularly how the length of exclusivity might decrease the number of medical breakthroughs but also the particular—I know many people hang on to the hope that something is going to be available to them for their own life-saving needs, and so these 2 aspects. Additional breakthroughs, follow-on behind some new discovery, often times they do, and then the part that relates to the patient's own survivability.

Ms. HARBOUR. I would say that the 12 to 14-year exclusivity period could in fact slow the pace of innovation so new—

Mrs. CAPPS. So other companies will know they just can't even do anything for that long a time so they won't try?

Ms. HARBOUR. That is right, and ultimately that is not good for the American consumer because you are not getting new drug products in the market as quickly.

Mrs. CAPPS. Right. I know especially because there are different criteria in other countries that sometimes people see availabilities in other places that they can't make available to themselves here, which creates quite a possible tragic situation at least from their points of view although to be sure we want to make sure that our standards are ones that we set ourselves. Is there any evidence on the previous—since I have just a few seconds left, that a long length of time of exclusivity would have this sort of chilling effect on additional innovations to that particular so upgrading it or making it better or doing something different along the side of it, sometimes different outcomes based on something that is set up in a particular—and they are very complex and they will spin off into some other kind of breakthrough?

Mr. WROBLEWSKI. We have seen in other areas that whenever the exclusivity ends that that is when the innovation occurs, and so to the extent that the follow-on pathway that you are establishing still keeps intact those very robust incentives of patent protection and market-based pricing then you will have the threat of competition coming from behind acting it is almost like carrots and sticks. With the carrot you have the ability to price at market whatever the market will bear for that period of time for your patent. And then you have the competition can come on and hasten the development. That is win-win for the consumers.

Ms. HARBOUR. And one thing I want to add. The exclusivity is really additional protection over and above what the patent system provides and the original rationale for the 12 to 14-year branded exclusivity period under Hatch-Waxman was to compensate for a perceived failure of the patent system. We haven't perceived that failure here with biologics and follow-ons.

Mrs. CAPPS. Thank you. I yield back.

Mr. PALLONE. Thank you. The gentleman from Utah, Mr. Matheson.

Mr. MATHESON. Thank you, Mr. Chairman. In my opening statement, I mentioned that 80 percent of the biotech industry right now remain unprofitable. Is that consistent with what you have heard as well?

Mr. WROBLEWSKI. We have seen the same statistics.

Mr. MATHESON. In the previous round of questions, you were asked for evidence about ability to attract capital. You mentioned recent stock performance and quarterly investment from venture funds. Do you think that short-term window of the last few months is really the best evidence you got for telling us that the investment incentives are right because I got to tell you that doesn't sell me.

Mr. WROBLEWSKI. Sure. We can certainly provide you all the evidence. We would be more than happy to give you the evidence.

Mr. MATHESON. Mr. Chairman, I think it would be real helpful again at future hearings, let us get some folks in the venture capital industry and let us get some other folks in here so we can have a broad discussion about what is really going on here because I do think we want to make sure when we are setting policy that we do set an environment that encourages that private sector investment in these areas. I think that would be a useful tool. I want to ask a question. Right now in Europe, you have heard, and a number of people said this in their opening statements, that it is 10 to 11 years of data exclusivity. Have you in your analysis thought about how an exclusivity period in the United States would be lower than the European model, how that would affect U.S. competitiveness in this industry?

Mr. WROBLEWSKI. The European model is very different for 2 reasons that we mentioned earlier. One was that the scope of the patent system is different in that they have regulated prices in Europe, so with a 10-year period of exclusivity and only the ability to charge a regulated price as opposed to a price that the market would bear, and if they have developed a monopoly, it is a monopoly price, that that market necessarily isn't—that model isn't necessarily as translatable here to the U.S.

Mr. MATHESON. Have you in your analysis, have you seen where a biotech industry is moving away from Europe and coming to the United States in previous years?

Mr. WROBLEWSKI. I think what we saw throughout the entire analysis was that biotech in many ways is a global industry, but that here in the United States it is locally centered, so because of the strong collaborative efforts between universities, between startups that have talent to manage projects that you have a collaboration, and so that is why you have in Wisconsin, you have a biotech industry—

Mr. MATHESON. Let me ask you, in your analysis did you look at why—in terms of looking why the Europeans set this data exclusivity at 10 to 11 years, you have mentioned your issue about market pricing, did you analyze other reasons why they set that exclusivity period where they did, and in fact was not one of the reasons because industries were leaving Europe and coming to this country?

Mr. WROBLEWSKI. When we spoke with the European regulators they explained that their system was kind of a different system because they were incorporating not only biologics but small molecule drugs too in that whole system and that it was a different dynamic than what I think we are facing here.

Mr. MATHESON. Let me ask you this question. Obviously, the committee is looking at different bills that look at data exclusivity. What are the factors you think we ought to be taking into consideration as a committee in terms of how we determine an appropriate length of exclusivity?

Mr. WROBLEWSKI. I think there are a couple of things that we should look at, one, to see if there is a failing in the patent system because drugs are unpatentable, that is a serious flaw for all drug development, and there should be some type of mechanism to recoup and to encourage people or firms to engage in that clinical testing.

Mr. MATHESON. So are you suggesting it is more of a patent reform issue and not data exclusivity, is that what you are saying?

Mr. WROBLEWSKI. Yes.

Mr. MURPHY. And you are saying that the fact the biologic industry maybe faces a different set of dynamics than conventional prescription drug industry that this exclusivity issue is not an appropriate tool for us to acknowledge the challenges in the biotech industry?

Mr. WROBLEWSKI. We didn't see that the tools that we currently used to incentivize innovation, basically patents and the fact that you can price up the market somehow would fail and with a bio-similar that wouldn't have nearly the dramatic market impact that a small molecule generic drug would have.

Mr. MATHESON. If you think that the intent is that we want to set up an appropriate opportunity for the private sector to recoup its R&D cost to develop one of these, are you telling me data exclusivity is not an appropriate tool for us to be looking at?

Mr. WROBLEWSKI. I think it is an appropriate tool to look at if the other 2 tools which have been wildly successful are broken.

Mr. MATHESON. And you are suggesting they are broken?

Mr. WROBLEWSKI. Quite the opposite. I am suggesting that they seem very strong.

Mr. MATHESON. I see my time has expired, Mr. Chairman, but I guess I will reiterate what a number of folks have said. I think it would be helpful to bring some other folks in before this committee to get some other points of view, and I will yield back my time.

Mr. PALLONE. Thank you. Before I ask Mr. Inslee, I know that my colleague from Georgia has a request.

Mr. DEAL. Yes, Mr. Chairman. I have a unanimous consent request that a report from Alex M. Brill, who is a fellow at the Amer-

ican Enterprise Institute, and a report from Lawrence L. Kotlikoff, Professor of Economics at Boston University, and a report from the ARP Public Policy Institute on biologics, that they be included in the record.

Mr. PALLONE. Without objection, so ordered.

[The information appears at the conclusion of the record.]

Mr. PALLONE. Mr. Inslee.

Mr. INSLEE. Thank you, Mr. Chairman. Thanks for allowing me to participate in this very important hearing, and I hope there are others on this line. This is a complex area, but there is one conclusion of this report that is so, in my view, fantastically unrelated to the realities of the marketplace. I really got to question it. On page 7 of your executive report, I will read you what it says. It says, "Central to each of these exclusivities is a public policy trade-off, a restriction on competition is provided in return for the development of a new drug product or new use of an existing product. A 12 or 14-year exclusivity period departs sharply from this trade-off because it does not spur the creation of a new biologic drug or indication. The drug has already been incentivized through patent protection and market-based pricing."

Now that statement is so fantastically unrelated to reality suggesting that the removal of the exclusivity period will help incentivize further investment in new drugs to cure new diseases. Right now if a drug company wants to go out there and develop a new drug that will cure leukemia, they have an incentive to invest in part because of data exclusivity, and yet you have turned that upside down and suggest by removing that data exclusivity somehow you will create an additional incentive for investment of a new drug. Now a biologically similar drug is not going to cure a disease that hasn't already been dealt with by the original product, and I just cannot fathom how you make this argument that removing data protection is going to create greater incentive for investors to put money into products that will truly respond to this condition in a new way. I just think you have turned reality on its head in that regard. So I will give you a chance to respond to that. I can't imagine what it would be but take a shot.

Ms. HARBOUR. Let me take a shot first. Your question seems to presume that the patent system is not strong enough to protect patents. Basically, exclusivity is additional protection above and beyond what the patent system provides.

Mr. INSLEE. But let me just ask you this. Don't you agree that data exclusivity is one of the things that investors take into consideration when they decide to plunk down several million dollars on something that may take a decade, that may or may not work? Don't you think that is an incentive for investment in truly new drugs that truly treat conditions in a new way, which is the original patent that we are talking about here? Don't you agree with that?

Ms. HARBOUR. No, only if there is truly a perceived failure with the patent system.

Mr. INSLEE. Well, then you do not have any, and with all due respect, any recognition of the investment climate in the United States if you do not recognize this as critical to inspiring investment in these truly new drugs. So let me ask you about that. Did

your study of valuing the impact on the investment in new products, truly new products, what will approach these conditions in a new way, did you evaluate how that would affect investment in these new products, and I mean new. That is not follow-on biologics. Did you?

Mr. WROBLEWSKI. We did not evaluate that in particular, and I will tell you why. It is because patent protection has been very, very strong. We have suggested though in the executive summary that one way to—

Mr. INSLEE. I have got limited time. I think if you would answer my question, I would appreciate it, but the point I want to make is you assumed for purposes of this study that there is no impact. That is an assumption we can't make because if you make that assumption and it is wrong, which I believe it is wholeheartedly wrong, you will cut off the development of new drugs because investments will not be made in them. So let me ask you a further question. Madam Commissioner, you told us you consider yourself an expert on consumers. I will give you a hypothetical consumer. Let us take parents of a 10-year old kid with leukemia, and we are now evaluating risks when we consider this legislation. One of the risks is that we would continue data exclusivity and the parents might have a 10 to 30 percent increased cost of a drug that might cure leukemia. Let us assume that there is one right now. The other risk is that a drug would never be created to cure leukemia because by removing data exclusivity the investment never gets made to provide that life-saving drug. As an expert in consumer behavior, what do you think is more important in the bigger risk to those parents of that kid?

Ms. HARBOUR. First of all, if I said I was an expert on consumers, I misspoke but let me—

Mr. INSLEE. I think that was the direct quote I could find.

Ms. HARBOUR. I am an expert on protecting the American—

Mr. INSLEE. OK. As an expert in protecting the consumer, what do you think would be a greater risk in the minds of the parents of that child, the risk that they would have a 10 to 30 percent higher cost for the drug or the risk that this drug that could cure their child would never be created?

Ms. HARBOUR. You are assuming that data exclusivity is the only way that one would invest in a drug, and that is what I am pushing back against. I don't think that assumption is correct. There are exceptions though where if you have a small patient population or if you are bringing drugs on the Orphan Drug Act where exclusivity would be necessary because there is a perceived market value, in that circumstance exclusivity would be absolutely appropriate.

Mr. INSLEE. And the unfortunate limitation of your study, according to what was just testified—

Mr. PALLONE. I just have to ask the gentleman—

Mr. INSLEE. Thank you, Mr. Chair. I appreciate your cooperation.

Mr. PALLONE. OK. The gentleman from Texas, Mr. Burgess.

Mr. BURGESS. Thank you, Mr. Chairman. Let me just follow along that discussion that you were just having. Now within the Federal Trade Commission, have you constructed a matrix that will give you a cost benefit analysis, some of the newer compounds, for

example, that inhibit some small blood vessel growth that may be used in treating more advanced cancers? Do you look at the number of hospital days that might be saved by using one of these advanced biologics and considering the cost? Yes, they are expensive but the disease that they are treating also has expensive consequences associated with it, so that if we avoid a surgery, if we avoid a week in the hospital, there are additional savings, not just the base line of the drug but there are other things to consider. So is there a matrix or a simulation or program that you use to help make those evaluations or is this simply data that is derived from the price tag on the bottle or box that the drug comes in?

Ms. HARBOUR. Those sort of questions sound like they are within the expertise of the FDA. We are looking at the——

Mr. BURGESS. I am so glad you brought that up because Mr. Chairman, we should be having this discussion with the FDA.

Ms. HARBOUR. And perhaps you will. We are your beginning act here, and we are talking about the competitive consequences of this sort of follow on. I believe there will be more hearings and discussions on these issues.

Mr. BURGESS. Now you and the FDA, are you aligned on your definition of things like bio-similar and bio-generic? Do you mean the same thing when you say those terms?

Mr. WROBLEWSKI. Yes.

Mr. BURGESS. It seems like the FDA has hinted that it might be otherwise, but you feel that currently there is a scientific basis for determining interchangeability of biologics from different and unrelated manufacturers?

Mr. WROBLEWSKI. What we tried to do was to say if there is an abbreviated pathway where the follow-on does not have to duplicate findings of safety and effectiveness because it can rely on the FDA's approval of the pioneer drug if that is allowed.

Mr. BURGESS. That is such a crucial question because the safety question can be very, very difficult to answer. And again just as an aside a week ago I was visiting the FDA and Dr. Hamberg and getting a tour with her through the new facility that they are occupying out there. One of the researchers just passing in the halls said what a difficult time they were having because of the viruses that might infect the cell cultures that are going to create these monoclonal antibodies that might be useful in the treatment of prevention of Alzheimer's in the future. Well, that is a pretty important arm or branch of that research. I don't know that he knows or would be interested if he could tell us that is this something that is so standard and so settled that you could do this in Dallas as well as Denver as well as Beijing and get the same result.

Ms. HARBOUR. That is very important, and that certainly would be for the FDA, not the FTC, to determine the safety and efficacy of these follow-on biologics.

Mr. BURGESS. Again, we are hitting on a recurrent theme, Mr. Chairman. We need to have a hearing that involves the FDA and many of us have been asking for that for some time. Again, I will just emphasize that I have not aligned myself with either of the 2 bills that are out there. I am really in an information gathering mode and safety had to be paramount for a doctor that picks up the pen and writes the prescription and rips it off and puts it in

the patient's hand and counsels them as to the risks and benefits. We have got to be able to provide them the best data. And it isn't always just the price tag on the box or the bottle that the medication is going to be delivered in.

What about, because this would come up all the time when I was a doctor, and I was in practice for years. There were some classes of medicines, and these were not biologics, these were just regular things, but there was some class of medicines there you just really didn't want to make a change and you didn't want a generic to be substituted and some of those things might be some of the cardiac drugs, certainly some of the diuretics that treat congestive heart disease, and in my practice estrogens from different manufacturers actually seemed to have a different biologic behavior. And I don't know whether it was the bio availability or the vehicle or what it was, but how are we going to address that? A doctor has got a patient who is on a very stable regimen, a patient with a serious and significant disease, and now a new bio-similar becomes available, how are we going to govern that because in the generic world it became harder and harder for me to control that, and often times I would have to pick up the phone and call 1-800 California and stay on hold for a long time to get my point across.

Mr. WROBLEWSKI. We couldn't agree with you more that those types of switching are going to be very difficult to do in the bio-similar environment, and that is one of the foundations that drew our conclusions that when a follow-on comes on to the market that its market impact is going to be substantially different than a generic drug, the market impact that a generic drug has.

Mr. BURGESS. Under the Waxman-Hatch, whatever it was, we lost the ability to—the provider, the doctor, lost the ability to control that, and again you had to really intervene on your patient's behalf if you didn't want to have a substitution.

Mr. WROBLEWSKI. And there is no similar type mechanism in—

Mr. BURGESS. Well, I think we heard that discussed this morning that there would have to be ways of directing this behavior because you couldn't always trust doctors to do the right thing, imagine that. Just one last point I will make. We heard the heparin tragedy a year ago in this very hearing room. The fact that often times the act of pharmaceutical ingredient, we only manufacture the compounds in this country but actually the active pharmaceutical ingredient may come from overseas, and the ability of the FDA to monitor those manufacturing facilities that are overseas, and again we saw a tragedy with heparin which is not a complex molecule. It is a little bit more complex than aspirin but it would not fall into this category. And we saw what happened with the intrusion of a foreign substance into that active pharmaceutical ingredient. It just seems to me that this manufacturing process which is fraught with much more peril, you got to be much more precise. You don't just line up the amino acids and say, there, I have made the protein. It is the folding, the unfolding, the sulphide bonds, hydrogen bonds, all those things are going to be critical to the biologic action of that product, and, again, all of which can be affected by the humidity, the atmospheric pressure, and goodness knows what else.

We have an obligation to protect—you say you are the advocate for the consumer. I think our first obligation has to be for the safe-

ty of that consumer, which is both the physician and the patient in that scenario.

Ms. HARBOUR. And as an advocate for consumers, I think it is a good thing to discuss all of these issues. We are here discussing the competitive implications. Obviously, the safety implications are paramount. You can't pass go if there aren't safety implications. There needs to be a hearing on this potentially as well, but here we can't opine on those. We don't have the expertise to opine on the safety. The FDA would have to do that.

Mr. BURGESS. Thank you for your testimony. Mr. Chairman, did you get that, we need to have a hearing with the FDA?

Mr. PALLONE. I have repeatedly said that we are having more hearings so no one is disagreeing with that notion, and I think it is pretty obvious that we have a lot of disagreements here and we need further hearings. Let me just thank both of you for being here. This has not been easy for you, but I appreciate your bearing with us. And, as I mentioned before, we will undoubtedly have members asking in writing for you to respond to questions. Normally that is about 10 days, and the clerk will notify you within the next 10 days of any written questions that the members would have. But I cannot stress enough that I think that this report was really informative for me and the other members, and appreciate your bearing with us today. Thank you very much. And without further adieu, this subcommittee hearing is adjourned.

[Whereupon, at 1:45 p.m., the subcommittee was adjourned.]

[Material submitted for inclusion in the record follows:]

Data Exclusivity Periods for Biologics:

Updating Prior Analyses and Responding to Critiques

Duke University Department of Economics Working Paper, No. 2008-10

December 22, 2008

Authors:

Henry Grabowski
Professor of Economics and Director of the Program in Pharmaceuticals and Health Economics
Duke University
grabow@econ.duke.edu
Corresponding Author

Genia Long
Managing Principal
Analysis Group, Inc.
glong@analysisgroup.com

Richard Mortimer
Vice President
Analysis Group, Inc.

Acknowledgments

This research was supported in part by the Pharmaceutical Research and Manufacturers of America (PhRMA). The design, analysis, and composition of the analyses and manuscript were conducted independently and entirely by the authors, and we are solely responsible for any errors.

The authors thank Alex Brill for sharing his data.

I. SUMMARY

Recent discussion, including at the November 21, 2008 Federal Trade Commission Roundtable on Follow-on Biologic Drugs, has addressed the question of the appropriate duration of data exclusivity (also called data protection) for innovative biologics. This paper proposes that the breakeven financial analysis outlined in an earlier paper is an appropriate framework for the assessment of different data exclusivity periods being proposed in the context of an abbreviated regulatory approval pathway for biosimilars.¹ Among the key parameters in this model are: the cost of capital;² expected margins produced by marketed biotech products (contribution margin);³ and other financial parameters such as required pre-marketing and post-marketing R&D investments. Applying this model led to the conclusion that a representative portfolio of biologics would “break even” or just cover its costs of development, manufacturing and sales, together with the industry’s cost of capital, in 12.9 to 16.2 years, thereby providing support for a substantial data exclusivity period.

A recent critique, which adopts the same model and framework for its assessment of the appropriate duration of data exclusivity periods, suggests that alternative values for the cost of capital and contribution margin parameters are more appropriate and that, applying them

¹ Grabowski, H., “Follow-on Biologics: Data Exclusivity and the Balance between Innovation and Competition,” *Nature Reviews Drug Discovery*, 7, 479 – 488 (2008).

² The cost of capital is the annual rate of return that an investor would require on average in order to make a given investment. In the case of biologics, this accounts for the risks associated with potential failure to develop or market the biologic candidate product successfully.

³ The contribution margin is a measure of how much a company earns in sales, after subtracting costs for labor and materials (cost of goods sold), and selling, general and administrative expenses. Contribution margin is not equivalent to profit margin, which also subtracts the costs of R&D, and interest, taxes and all other expense items.

supports a lower breakeven period, and therefore, a lower data exclusivity period.⁴ It also considers the effects on breakeven periods of different assumptions for innovator product share and price impacts resulting from biosimilar entry. This paper corrects computational problems and inconsistencies in Brill's critique of the breakeven period. Furthermore, it disputes his claim that a 10% cost of capital and an average 60% contribution margin assumption are reasonable and appropriate baseline values, and performs a number of sensitivity analyses using a range of input values. Together, these analyses suggest that limiting the data exclusivity period to less than 12 to 16 years results in failure of the representative portfolio of biologics to break even within an extended period, under reasonable assumptions.

The remainder of this paper is organized as follows:

- **Section II** discusses the importance of data exclusivity to biologics, including why patents alone may be insufficient to provide protection for biologics;
- **Section III** summarizes why the portfolio cash flow approach adopted in this paper is an appropriate framework for analysis of the impact of data exclusivity limits on investment and competition in the biotech industry;
- **Section IV** summarizes the key points in a recent critique of the previous "breakeven" analysis published in *Nature Reviews Drug Discovery* (hereafter referred to as the *Nature* model) and identifies four problems and implausible assumptions in this critique;
- **Sections V and VI** refute key assumptions from this critique, including the a cost of capital that is too low (Section V) and contribution margins that are too high (Section VI);
- **Section VII** notes that the critique fails to take into account other countervailing assumptions in the prior *Nature* analysis that tend to understate expected breakeven periods;
- **Section VIII** extends the previous *Nature* analysis to incorporate other impacts associated with biosimilar entry, and summarizes the results of sensitivity analyses on the extended model;
- **Section IX** summarizes the overall results of the additional analysis in this paper; and
- A brief **Appendix** addresses the critique's computational inconsistencies

⁴ Brill, A., "Proper Duration of Data Exclusivity for Generic Biologics: A Critique," unpublished manuscript, November 2008.

II. THE IMPORTANCE OF DATA EXCLUSIVITY TO BIOLOGICS

Data exclusivity is the period of time between FDA approval and the point at which an abbreviated filing for a biosimilar relying in whole or in part on the innovator's data on safety and efficacy can receive final approval. Data exclusivity is designed to preserve innovation incentives, and recognize the long, costly, and risky process necessary for the innovator to gain FDA approval. Data exclusivity is a critical issue for the future of biologics, with different provisions for data exclusivity in recent legislative proposals ranging from zero to 14 years. All bills other than H.R. 1038, sponsored by Representative Henry Waxman of California, proposed combined periods of at least 12 years.^{5, 6}

Data exclusivity periods are essential to compensate for some important shortcomings in patent protection for biologics. Data exclusivity extends from the date of product approval, and this protection period runs concurrently with any remaining patent term protection for the biologic. That is to say, data exclusivity provides additional protection to the innovator when the remaining patent length is shorter than the data exclusivity period at the time of approval (which can occur due to lengthy preclinical and clinical research required to obtain FDA approval), or to

⁵ Although H.R. 1038 contains no data exclusivity period at all, its absence did not necessarily indicate opposition to a provision, according to coverage at the time, but rather a desire to hold off on backing a specific figure until more was learned about what an appropriate period should be. See summary in *Inside Health Policy*, "Boston University Study Criticizes Exclusivity Measures in Biogenerics Bills," September 30, 2008. Access October 29, 2008 at www.insidehealthpolicy.com/secure/health_docnum.asp?f=health_2001.ask&docnum=9302008_boston&DOCID=9302008_boston.

⁶ Recent legislative proposals for establishing an abbreviated pathway for biosimilar entry consider both permissible filing dates and overall market protection periods. For example, the bill S.1695, sponsored by Senator Kennedy, allows for four years before an abbreviated filing can occur, during which the FDA cannot rely on innovator's data on safety and efficacy to review an abbreviated biosimilar application, followed by an additional eight years during which FDA review of the application can take place but the application cannot be approved, for a total of 12 years of data exclusivity.

the extent that the patent is circumvented by a biosimilar prior to its expiry. Patent protection alone may be insufficient for biologics in the context of biosimilars for two primary reasons:

(1) The standard for FDA approval of biosimilars is likely to be based on *similarity* rather than *sameness*, allowing for greater differences between the biosimilar and the reference product than are allowed between an AB-rated generic small-molecule drug and its reference product. As a result, development of a biosimilar may allow for greater deviations from the reference product and greater opportunity to deviate slightly from the patented technology, thereby sidestepping patent infringement while still benefiting from an abbreviated FDA application process. In 2007 remarks before the Committee on Oversight and Government Reform, Dr. Janet Woodcock of FDA noted, “Because of the variability and complexity of protein molecules, current limitations of analytical methods, and the difficulties in manufacturing a consistent product, it is unlikely that, for most proteins, a manufacturer of a follow-on protein product could demonstrate that its product is identical to an already approved product.”⁷

(2) Patents for biologics, unlike for small-molecule drugs, do not typically protect the entire molecule or class of related molecular structures. Biologics are much more complex than small-molecule drugs, and the patents protecting biologics tend to focus on certain aspects of the protein or ways of producing the protein rather than on protecting the entire molecule.⁸

Data exclusivity provides investors with an “insurance policy” against the potential failings of patent protection for biologics. Recent evidence suggests that the effective marketing

⁷ Woodcock, J. “Follow-on Protein Products” Statement before the Committee on Oversight and Government Reform, U.S. House of Representatives, 26 March 2007, FDA web site (online), <http://www.fda.gov/oc/2007/rotein32607.html>. (2007).

⁸ Manheim, H., Granaham, P., and Dow, K., “Follow-on Biologics: Ensuring Continued Innovation in the Biotechnology Industry,” *Health Affairs*, 25:394-404 (2006).

exclusivity period for small-molecule drugs (the time between launch and first generic entry) is approximately 12 years on average.⁹ Data exclusivity for small-molecule drugs is generally not the constraint on generic entry (although in recent years, it has become increasingly important for small molecules due to the rise of Paragraph IV challenges under the Hatch-Waxman Act), whereas it is expected to be more determinative for biologics due to the nature of their patent protection.¹⁰

III.A PORTFOLIO DISCOUNTED CASH FLOW APPROACH IS AN APPROPRIATE FRAMEWORK FOR ANALYSIS OF THE IMPACT OF DATA EXCLUSIVITY LIMITS ON INVESTMENT AND COMPETITION IN THE BIOTECH INDUSTRY

In evaluating the impact of data exclusivity periods of different durations on the incentives for innovation, an appropriate perspective to adopt is that of a potential investor who weighs alternative investments, together with their expected risks, costs and returns. Venture capital and private equity are the primary sources of early stage investment in biotech start-ups, which account for many new pipeline biologics. Venture capital-backed firms constitute 40 percent of employment in biotechnology.¹¹ Such investors account for the low probabilities of success of any individual opportunity by investing in a long-term portfolio of opportunities, most of which ultimately will not succeed, but one or two of which may earn significant returns years later. Larger established firms, as well as venture investors, need to take a portfolio approach,

⁹ Grabowski, H. and Kyle, M., "Generic Competition and Market Exclusivity Periods in Pharmaceuticals," *Managerial and Decision Economics*, 28: 491-502 (2007). For drugs with first-generic entry in 2005, the average market exclusivity period (MEP; the time between product launch and first-generic entry) was 11.5 years (drugs with sales greater than \$100 million) to 13.0 years (all drugs).

¹⁰ Grabowski, H. "Are the Economics of Pharmaceutical R&D Changing? Productivity, Patents, and Political Pressures," *PharmacoEconomics*, Vol. 22, Suppl. 2, 2004, pp. 15-24.

¹¹ Lawton R. Burns, Michael G. Housman, and Charles A. Robinson, "Market Entry and Exit by Biotech and Device Companies Funded by Venture Capital," *Health Affairs* 28, no. 1 (2009): w76-w86.

given the low probability of success for new biological candidates, and the skewed distribution of sales revenues for approved marketed candidates. Venture capital firms use discount rates that vary by stage of investment, and account for a decreasing level of risk as products approach launch and commercialization. An empirical analysis of this issue found that discount rates vary from 70% down to 25%, depending on stage of finance (start-ups to IPOs).¹² Similarly, established biotech or pharmaceutical firms apply a portfolio approach to their selection of which candidate molecules to advance in development and to the valuation of licensing and acquisition opportunities, using a risk-adjusted cost of capital, as discussed below.

This approach was outlined in an article recently published in *Nature Reviews Drug Discovery* (Grabowski, 2008; henceforth referred to as the *Nature* article). In a recent unpublished white paper, Alex Brill utilizes the same framework to comment on the optimal data exclusivity period. Brill accepts the basic premise of the *Nature* article, namely that data exclusivity times should be guided by the time necessary for a representative new biological entity to just cover its expected R&D, sales and marketing investments, together with the industry-wide cost of capital. This is defined as the “breakeven lifetime” in the parlance of economics and financial studies.

Brill also accepts the appropriateness of a portfolio approach to evaluating R&D investment decisions, like the one performed in the analysis in the *Nature* article. Accordingly,

¹² Sahlman, W.A., “The Structure and Governance of Venture-Capital Organizations,” *Journal of Financial Economics*, 27(1990) pp. 473-521, Table 6 at p. 511.

he also focuses on the returns for a representative biological product from a portfolio based on the historical distribution of R&D costs and revenues.¹³

IV. BRILL'S ANALYSIS

As discussed, the analysis presented in the 2008 *Nature* article results in breakeven returns for the representative biologic between 12.9 years and 16.2 years. This is depicted in Exhibit 1, which is Figure 7 from the *Nature* article. This diagram shows the cumulative net present values over a 30-year period from the beginning of the R&D investment period through market launch and over the product life cycle. As shown in this diagram, it takes 12.9 years after launch, at a discount value of 11.5%, for the cumulative net present value (NPV) to become positive in terms of value from cash flow, and 16.2 years for breakeven at a discount value of 12.5%. Alternatively stated, it takes 12.9 to 16.2 years for the firm to earn a rate of return which is just equal to its risk-based cost of capital.

A. DESCRIPTION OF BRILL'S ANALYSIS

In his white paper, Brill makes three changes from the analysis presented in the *Nature* article that affect the breakeven point calculation:

¹³ In particular, his basic inputs include average R&D investment from DiMasi and Grabowski, 2007 (DiMasi, J., and Grabowski, H., "The Cost of Biopharmaceutical R&D: Is Biotech Different?" *Managerial and Decision Economics*, Vol. 28, Issue 4-5, pp. 469-479), sales revenue distribution for biologics based on Grabowski, 2003 (Patents and New Product Development in the Pharmaceuticals and Biotechnology Industries," *Science and Cents*, edited by John Duca, Federal Reserve Bank of Dallas, 2003, pp. 87-104), and post approval R&D costs and product launch expenditures based on Grabowski, Vernon and DiMasi, 2002 (Grabowski, H., Vernon, J., DiMasi, J., "Returns on Research and Development for 1990s new Drug Introductions," *Pharmacoeconomics*, Vol. 20, Supplement 3, 2002, pp. 11-29).

(1) First, he assumes that the innovator's product will retain a significant share of its pre-entry sales after the market entry of biosimilars, and bases his estimates in this regard on recent assumptions from the Congressional Budget Office (CBO).¹⁴

(2) Second, he utilizes a 10% baseline real cost of capital for the representative biotechnology firm, compared to the 11.5% to 12.5% range utilized in the *Nature* article.

(3) Third, he utilizes a 60% contribution margin for the representative biologic product, compared to a 50% baseline value in the *Nature* article.

The *Nature* article estimates a breakeven lifetime of between 12.9 and 16.2 years for the representative biological product. With the above changes in assumptions, Brill claims that relatively short exclusivity periods would still be compatible with significant innovation incentives. In particular, he claims that a seven-year data exclusivity period with subsequent biosimilar entry would still allow firms to break even in just over ten years.

However, Brill's analysis is subject to computational problems and inconsistencies, as well as implausible assumptions. When these are corrected and accounted for, his implication that short data exclusivity periods, coupled with rapid biosimilar entry, still provide strong innovation incentives is not valid. In this paper, we perform alternative sensitivity analyses on particular inputs and assumptions, and confirm the importance of a substantial data exclusivity period for biologics.

¹⁴ Congressional Budget Office, Cost Estimate: S.1695 Biologics Price Competition and Innovation Act of 2007, June 25, 2008.

B. CRITIQUE OF BRILL'S ANALYSIS

Exhibit 2 is taken from Brill's white paper (it is Figure 3 in his paper and appears with results uncorrected). This exhibit uses the same framework as Exhibit 1, but reflects the changes Brill implemented to incorporate biosimilar entry (including his calculation errors and implausible assumptions). In particular, for the specific case presented in this exhibit, there is a hypothesized data exclusivity period of seven years, after which biosimilars are assumed to enter. Brill relies on a discussion of shares and prices from the CBO bill-scoring document to make assumptions on innovator share and price erosion following biosimilar entry. Brill assumes that, on average, biosimilars will capture a 10% share of the market in the first year of entry, growing to a steady state of 35% within 4 years. He further assumes that price (sales-weighted) would decline by 20% in the first year, and reach a steady state of a 40% price discount by the fourth year. The analysis is also performed under Brill's assumption of a 10% cost of capital and a 60% contribution margin. As shown by the dotted line in this diagram, Brill finds the firm can still break even in year 10, and earn increasingly positive cash flow values after that point.

The four problems and implausible assumptions in Brill's analysis are:

(1) *Brill's calculations include a significant computational problem and inconsistency in incorporating assumptions made by the CBO in its scoring of follow-on biologics bill S. 1695 into the Nature model; correcting these problems does not yield his results as reported and does not support a seven year data exclusivity period.* Since the publication of the *Nature* article, the CBO has published a bill-scoring estimate that includes some discussion of potential market shares and price discounts with biosimilar entry. Brill references the CBO discussion in his assumptions of biosimilar shares and price discounts, which

are used to evaluate whether particular data exclusivity periods are compatible with eventual breakeven returns. In doing so, however, the treatment of price discounts and margin changes in Brill's analysis are inconsistently incorporated into the investment returns model in the *Nature* article. This in turn results in a significant underestimation of breakeven times.

(2) ***Brill's assumption on the cost of capital is not reasonable and is at odds with most current best thinking on the subject and with other commonly used industry metrics.***

Indeed, the most sophisticated analysis in the current literature, together with accepted published industry metrics, suggests real costs of capital for biotech firms are well above the 11.5% to 12.5% assumed in the *Nature* article. (Golec and Vernon, 2007; Ibbotson Annual Cost of Capital Yearbook, 2008)¹⁵ Brill also fails to acknowledge the large subsample of private and public biotech firms without marketed products that need to rely on venture funding and financial instruments at very high costs of capital.

(3) ***Brill's assumption for the average contribution margin relies on results from six of the most profitable biotech firms, and fails to consider the high degree of variability in profits even among this small, upwardly biased sample. His approach also puts inordinate weights on two of the most successful biotech firms***¹⁶. As a result of these sample selection issues, his 60% margin can be viewed as being an extreme value, or upper bound, rather than being a plausible baseline value.

¹⁵ Golec, J., and Vernon, J., "Financial Risk in the Biotechnology Industry," *Journal of Applied Economics and Health Policy*, forthcoming; also NBER Working Paper # 13604, November 2007. Ibbotson, *Cost of Capital Yearbook*, Morningstar, 2008.

¹⁶ Together, Amgen and Genentech alone receive 67 percent of the overall weights in Brill's calculation of the average.

(4) *Brill ignores countervailing assumptions already reflected in the Nature article breakeven analysis, which have the effect of producing estimated breakeven periods that are shorter than likely actual breakeven periods.* For example, the representative portfolio modeled reflects the mean values observed for only the top four ranked quintiles of the sales distribution of established biotechnology drugs, with the bottom quintile excluded. Excluding all biologics in the lowest tail of the distribution biases breakeven periods downward. In addition, the *Nature* model assumes that firms can use existing plant assets to produce the biologics in the modeled portfolio at commercial scale and that capital costs are captured fully by depreciation charges subsumed in the contribution margin. This approach also biases breakeven periods downward, as some new plant construction or retrofitting would be required. The cost of a new multi-product manufacturing plant for large-scale commercial production is substantial. It has been estimated elsewhere that a new manufacturing plant can take three to five years to construction and can cost \$250 million or more.¹⁷ Even retrofitting existing plant assets can cost between \$50 and \$100 million. Finally, the *Nature* model assumes a 3.5% reduction in branded biologic share each year, beginning in the 10th year to account for therapy obsolescence. Vigorous dynamic competition in the therapeutic areas with high unmet need (such as rheumatoid arthritis, oncology and other areas) typically served by biologics, and the high numbers of pipeline products in these areas suggest actual rates of share attrition may be higher in the coming years.

¹⁷ Molowa, D.T. The State of Biologics Manufacturing. J.P. Morgan Securities, Equity Research Healthcare Note. 16 February 2001.

C. CORRECTING LOGICAL INCONSISTENCIES IN BRILL'S ANALYSIS

Brill's first point concerning innovator sales after biosimilar entry can be viewed as a logical extension or sensitivity analysis to the breakeven analysis. In the *Nature* article, various qualifying points that had countervailing effects on the breakeven lifetime were presented.¹⁸ One such qualifying point was that, for the foreseeable future, innovative firms may retain significant shares of the market after the entry of biosimilars. This is in contrast to the current experiences of small-molecule drugs, where as behavior under Hatch-Waxman has evolved over the years, high sales products now often lose 90 percent of the market to generics within just a few months (Grabowski, 2004; Silver, 2008).¹⁹ Over time, the markets for biosimilars may evolve to more closely resemble the now intensely competitive ones for generic chemical entities (Grabowski, Cockburn and Long, 2006).²⁰ In the meantime, however, current biologics may be able to earn potentially significant revenues after biosimilar entry, prolonging the innovative product's life beyond the expiration of data exclusivity periods. Therefore the impact of innovator sales and price erosion on the breakeven calculation needs to be further investigated.

Brill's analysis of these issues, however, has inconsistently implemented how the price erosion assumption will affect the model results presented in the *Nature* article. In calculating changes in contribution margins, Brill assumes that the innovator will discount the price of the brand biologic in response to biosimilar entry, by the same amount as the sales weighted price of

¹⁸ Most of the other qualifying points in Grabowski (2008) operate in an opposing manner as discussed below, and these points were ignored by Brill.

¹⁹ Grabowski, H., "Are the Economics of Pharmaceutical R&D Changing? Productivity, Patents and Political Pressures," *Pharmacoeconomics*, Vol. 22, Suppl. 2, 2004, pp. 15-24. Silver, R., "A Wall Street Perspective on Generics," 2007 GPhA Annual Meeting, March 1-3, 2007, available at <http://www.gphaonline.org/AM/CM/ContentDisplay.cfm?ContentFileID=593>.

²⁰ Grabowski, H., Cockburn, I., Long, G., "The Market for Follow-On Biologics: How Will it Evolve?," *Health Affairs*, 25, no. 5 (2006), pp. 1291-1301.

the biosimilar entrants. However, he fails to correspondingly reduce the level of assumed brand biologic sales in his modification to the model by the same price discount. This inconsistent computational approach means that he multiplies margins that take the price erosion assumptions into account by revenues that do not.²¹

As discussed in the sensitivity analysis later in this paper, Brill's interpretation of the CBO assumptions on the brand's price response is open to question. The CBO report states that biosimilar entry will constrain innovator prices, but does not specify by how much it will do so.²² Hence, this is a subject for further sensitivity analysis that we undertake in Section VIII. In this section, however, we examine the effects of the logical inconsistency in Brill's analysis, given his interpretation that the innovator price will be the same as the sales weighted average of the biosimilars. Further details and an illustrative example of this computational problem are presented in the Appendix.

Correcting Brill's computational problems and inconsistencies has a substantial impact on his findings. Applying his overstated baseline profit margin assumption of 60% and understated baseline cost of capital assumption of 10% to the corrected model, and maintaining his assumption of a seven-year exclusivity period results in a breakeven period of over 13 years, not the just over 10 years that he reports. Furthermore, he erroneously states that even with a cost of capital of 11.5% and a seven-year exclusivity period (and his other assumptions

²¹ These issues are discussed more specifically in the Appendix to this paper. In the updated *Nature* model calculations presented in this paper, we assume that costs are reduced proportionately with reductions in output.

²² In a telephone conversation on December 22nd, CBO confirmed that the appropriate interpretation of the assumption in their report that the availability of biosimilars will constrain brand-name prices is that brand-name prices will be lower than they would otherwise be without any biosimilar entry. However, the CBO has not released any quantitative assumptions in this regard and are still analyzing the issue in light of new information.

unchanged), a breakeven period (of unspecified magnitude) results. In fact, when his calculation error is corrected, there is no breakeven period in the first 50 years when applying an 11.5% cost of capital assumption and a seven-year breakeven period.²³

D. SENSITIVITY OF BRILL'S RESULTS

After correcting for calculation problems and inconsistencies, Brill's findings are extremely sensitive to small changes in his assumptions. Exhibit 3 uses the same framework as Exhibit 2, but corrects for Brill's calculation error. Using reasonable assumptions, a seven-year exclusivity period is insufficient:

- Keeping all of his assumptions unchanged but reducing the margin assumption from 60% to 55% results in *no breakeven period within the first 50 years*.
- Similarly, increasing just his cost of capital assumption from 10% to 11.5% (and keeping his margin assumption at 60%), again results in *no breakeven period within the first 50 years*.

Even if Brill's margin and cost of capital assumptions were reasonable, which they are not, such high sensitivity in findings to small changes in those assumptions would be of significant concern.

It is also important to keep in mind that while biosimilar penetration rates and/or brand price discounts may be modest in the near term (as reflected in estimates for existing products by

²³ Whether or not a breakeven period exists beyond 50 years following launch of the brand was not investigated, as it is unlikely that investors will consider projects with such a lengthy term to break even regardless of the discount rate.

the CBO or others), they could very well exceed those assumed by Brill in the longer run.²⁴

Data exclusivity provisions are focused on innovation incentives for the long-term. Many of these molecules will not reach the market for a decade or more, and biosimilar entry will be even further removed in time from market launch. Over time, attrition rates may increase for biologics as the FDA develops a larger experience base, and private and public reimbursement systems evolve for biosimilars.

Even if one accepts Brill's cost of capital and contribution margin assumptions, increasingly aggressive biosimilar entry following the expiration of data exclusivity periods would result in longer breakeven periods over time or no breakeven period at all over a reasonable timeframe.

V. 10 PERCENT COST OF CAPITAL IS NOT CREDIBLE FOR BIOTECH FIRMS

The *Nature* article's estimates of the real cost of capital, 11.5% and 12.5%, are substantially below reliable broad industry estimates of the cost of capital for biotech R&D investments. These original estimates were based on a small group of biotech firms that had multiple FDA-approved biologics and a history of positive operating profits over the past decade, and understate cost of capital for the industry more broadly, which includes smaller biotech firms with few or no biologics on the market. As noted in the *Nature* article, for these reasons, the values used for the real cost of capital are conservative, meaning they are below those faced by most firms. In addition, recent best academic literature estimates the real cost of capital for

²⁴ The CBO's estimate focuses on a 10-year timeframe beginning with the present when the initial implementation of a regulatory pathway for biosimilars would be developed and implemented and the first biosimilars would enter the market.

biotechnology firms to be no lower than 13.25%, and in some cases much higher when the focus is small to mid-size biotechnology firms:

- Golec and Vernon (2007) estimate costs of capital for the biotechnology industry generally, relying on a three-factor Fama French model (as opposed to a CAPM model), which is the generally accepted, appropriate methodology for estimating cost of capital.²⁵ Golec and Vernon (2007) estimate a nominal cost of capital of 16.75% for biotech R&D investment, and Vernon recently noted that this corresponds to a real cost of capital of 13.25%, significantly higher than the 11.5% and 12.5% figures used in the *Nature* models.²⁶
- Ibbotson's Cost of Capital 2008 Yearbook, a widely accepted general industry source for cost of capital estimates, reports a similar nominal three-factor Fama-French estimate of 17.49% for the median publicly-traded company within the biotechnology SIC code (2836). Assuming a 3% annual inflation rate, this figure would correspond to a 14.07% real cost of capital.

²⁵ Fama-French three factor return models are considered to be far superior for estimating cost of capital in industries such as biotechnology. As noted in Golec and Vernon (2007), the finance literature has established that "[s]ingle factor models such as the Capital Asset Pricing Model (CAPM) do not capture all of the types of systematic risk that influence firm cost of capital. In particular, the CAPM does not reflect the empirical evidence that supports both a size-related and a book-to-market related systematic risk factor."

²⁶ As estimated by Vernon in comments filed with the FTC during its comment period. This is consistent with Myers and Shyum-Sunder, 1996 (Myers, S., and Shyum-Sunder, L., "Measuring Pharmaceutical industry risk and the cost-of-capital," In: RB Helms, editor, *Competitive Strategies in the Pharmaceutical Industry*, Washington, DC, AEI Press (1996), pp. 208-237), who estimate a 14% real cost of capital for seven medium-sized publicly traded biotech and pharmaceutical firms for 1989. Brill cites this paper, but neglects to mention the 14% estimate in the paper or their corresponding analysis of "small" firms (including Biogen, Cetus and Genentech, along with other firms like Scherer and Mylan, with lower average betas than the true biotechs); the small firm sample had real equity costs of capital of 16.1% (p. 228), and higher if one just used biotech firms.

- Grossman (2003) estimates the cost of capital for smaller biotechnology firms and finds that biotechnology firms without a marketed product but with one or more biologic candidates in Phase II or III trials have an average nominal cost of capital of 27.4%.²⁷ He also estimates a nominal cost of capital for biotechnology firms with at least one biologic approved of 18.17%.²⁸ Again assuming a 3% annual inflation rate, these figures would correspond to real costs of capital of 23.69% and 15.24%, respectively.

Consistent with these findings, many small biotechnology firms rely heavily on venture capital for financing, which typically implies very high cost of capital requirements, and biotechnology firms are facing increasing difficulties obtaining this financing in the face of the current credit crunch.²⁹ Table 1 summarizes biotechnology industry cost of capital figures from a wide range of sources.

Brill relies on a real cost of capital of 10%, which is far lower than estimates typically reported in the academic or trade literature for the biotechnology industry. His results are also highly sensitive to increases in this estimate.³⁰ Brill claims to substantiate his 10% cost of

²⁷ Grossmann, M., *Entrepreneurship in Biotechnology*, Physica-Verlag New York, 2003.

²⁸ Myers and Howe (1997) similarly find that smaller biotech firms had much higher betas (measures of risk) than larger biotech companies, which would result in substantially higher cost of capital for smaller firms. They estimate an average beta in 1992 of 1.38 for "mature" biotech firms, 2.38 for biotech firms with drug candidates in advanced stages of clinical testing, and 2.17 for biotech firms without drug candidates in advanced stages of clinical testing.

²⁹ See for example, Boyle, C., "Credit Crunch Threatens Investment in Medicines," TimesOnline, October 27, 2008.

³⁰ Brill's claim in footnote 9 of his paper that breakeven still occurs with a cost of capital of 11.5% and a 7 year data exclusivity period is not accurate (even if one relies on his assumed 60% profit margin). Prior to correcting for errors in Brill's calculations, his model yields a 17 year breakeven period with a cost of capital of 11.5% rather than 10%; after correcting the calculations in his model but keeping all inputs other than cost of capital unchanged there is no breakeven in the first 50 years.

capital assumptions by citing the paper, DiMasi and Grabowski (2007), along with Myers and Shyam-Sunder (1995), and by citing a website maintained by Damodaran:

- Brill's interpretation of DiMasi and Grabowski,(2007) as being consistent with a 10% cost of capital is not correct. The 10% estimate is the lowest of several estimates found (other estimates included 12 and 12.5%) and reflects a period of low risk-free rates and risk premiums. Investors will consider *long-term* investment conditions, however, and the lower observed short-term period of risk-free rates and risk premiums are unlikely to be a reliable guide as to long-term future rates and premiums. Furthermore, the estimate is based on relatively large, publicly traded biotech and pharmaceutical companies and does not reflect the cost of capital of small or mid-sized biotechs.
- In discussing DiMasi and Grabowski (2007), Brill also cites Myers and Shyam-Sunder (1995), but ignores their 1989 analysis of "small" firms that finds a real equity cost of capital of 16.1%, or even higher if one examines just biotech firms. Their "small" firm sample actually includes several well-established companies that are now leaders in the biotech field.³¹
- Using data on a website maintained by Damodaran, Kotlikoff (2008) finds the real cost of capital as of January 2008 to be 12.7% for biologic firms. To calculate this cost of capital he uses a risk-free rate based on U.S. Treasury inflation protected securities ("TIPS") of 2%. Brill relies on the same data but estimates a real cost of capital of 10.25%, apparently suggesting that Kotlikoff's estimates are overstated. To arrive at a lower cost of capital than Kotlikoff, it is likely the case that Brill is assuming a lower

³¹ Such as Biogen and Genentech, along with other firms like Scherer and Mylan with lower average betas than the true biotechnology firms.

risk-free rate and a lower equity premium. In fact, Brill's risk-free rate would need to approach zero to account for the difference between his and Kotlikoff's cost of capital estimates, as the other input data currently available from Damodaran's website appear to be unchanged from those relied on by Kotlikoff.³² Biotech firms and early stage investors cannot and do not change their R&D investment decisions based on monthly changes in U.S. Treasury rates, however, as would be suggested by Brill's analysis of the Damodaran data. In comparison, the 13.25% real cost of capital estimate found by Golec and Vernon (2007) reflects a superior approach that is longer-term in focus and less susceptible to such volatility.

Relying on cost of capital inputs that do not accurately reflect the actual biotech industry cost of capital to determine an exclusivity period risks adverse effects on financing. This would severely restrict investment in the development of new therapies and have a potentially strong negative effect on competition. As discussed earlier, the costs of capital for firms without marketed products exceed the industry average substantially and would be particularly adversely affected.

³² The sample of companies that Damodaran relies on for the biotechnology industry includes a number of firms that are not true biotechs for the purposes of this paper, including: Luminex, a bioassay testing firm; Martex Biosciences, which markets supplements; Ista, primarily focused on small molecule ophthalmic products; and Mamatech, which develops breast tumor detection products.

VI. CONTRIBUTION MARGINS OF 60 PERCENT ARE TOO HIGH AND REFLECT THE EXPERIENCE OF ONLY A FEW OF THE LARGEST AND MOST SUCCESSFUL FIRMS

The *Nature* article simulations rely on a 50% contribution margin,³³ which is based on the contribution margins realized by the eight largest biotech firms with multiple products on the market. However, few biotech companies are actually profitable, and the universe of biotech firms is populated with development-stage companies whose principal assets are their human capital and intellectual property. These companies would be expected to experience lower contribution margins than a firm with an established line of approved products as represented by the sample that reflects even a 50% margin.

Brill argues for a much higher contribution margin of 60%, which is not reflective of the expected profit potential for most biotechnology products. He bases this estimate on a market-capitalization-weighted average of large and very successful companies, which has the effect of biasing his figure upward and is not representative of the sector.

Brill's use of market-capitalization weighting means that his average margin primarily reflects just two biotech firms with large market capitalizations relative to the other firms in his sample. Even among Brill's six highly successful companies, many of them earn margins well below his 60% average, and there is considerable variation in margins from 43.4% to 63.7%.

³³ As noted earlier, the contribution margin is a measure of how much a company earns in sales, after subtracting costs for labor and materials (cost of goods sold), and selling, general and administrative (SG&A) expenses. It is expressed as a ratio of sales, less cost of goods sold and less SG&A, to sales. Contribution margin is not equivalent to profit margin, which also subtracts the costs of R&D, and interest, taxes and all other expense items. All calculations of the contribution margin in this paper were based on publicly available sources.

Furthermore, three of the six firms identified by Brill earn margins of 50% or less over the 2001 to 2007 time period that he examines.

Two of the largest biotechnology not identified in Brill's sample that qualify for inclusion and were independent firms during the time period examined earned average margins of 36% and 35%, respectively, during the 2001 to 2007 period, substantially lower than Brill's 60% margin assumption.³⁴ Including these two additional firms, the range in margins over the time period would be 33.6% to 63.7% with five of the eight biotechnology firms reviewed earning margins of 50% or less.

Not only do a number of highly successful biotech companies fail to earn contributions margins consistent with his 60% assumption, but contribution margins for medium and smaller biotechnology companies would also be far lower than 60%.

Relying on Brill's overly optimistic contribution margin assumption to determine appropriate exclusivity periods for biologics would result in estimated breakeven periods that are too low. If these figures are used to determine data exclusivity period limits, it would have the effect of making investment in some potentially important innovative biotech products too unattractive to warrant the cost and risk of investment..

VII. BRILL HAS IGNORED OTHER COUNTERVAILING ASSUMPTIONS IN THE PRIOR *NATURE* ANALYSIS

The *Nature* analysis imposes a number of countervailing assumptions that are likely to overstate expected revenues and understate expected costs, resulting in breakeven periods that err on the side of being shorter than what would actually be experienced in the biotechnology

³⁴ These firms are MedImmune and Chiron.

industry. Brill fails to note any of these countervailing assumptions in his critique, or the fact that reasonable alternative assumptions result in longer breakeven periods, and potentially no breakeven point using his cost of capital, contribution margin, and seven-year data exclusivity assumptions. These countervailing assumptions include:

(1) ***The lowest quintile of sales is excluded when estimating the expected average revenue stream.*** Excluding the lowest quintile results in estimates that potentially overstate expected revenues, and understate expected breakeven periods.

(2) ***A very low rate of product obsolescence from new biologics is assumed.*** Specifically, the *Nature* model assumes no product obsolescence in the first 10 years following release, and only a 3.5% annual reduction in sales after 10 years. The recent surge in the biologic product pipeline and R&D growth for biologics suggests that a faster rate of new product introduction, and therefore a higher rate of obsolescence (shorter product life cycles) may apply than that assumed in the *Nature* model. Currently, over 600 biologics are in development.³⁵ This low rate of product obsolescence further serves to potentially overstate the expected revenue stream from successful biologics. Including the effect of more robust brand-to-brand competition would produce longer required breakeven periods.

(3) ***Finally, the Nature model assumes that firms are able to utilize existing plants with no retrofitting costs.*** The *Nature* model assumes that product validation costs are the only costs required to produce successful biologic products. In actuality, many firms may face

³⁵ The Pharmaceutical research and Manufacturers of America (PhRMA). Medicines in Development – Biotechnology 2008. PhRMA web site (online), <http://www.phrma.org/images/110308%20biotech%202008.pdf> (2008).

substantial upfront capital investment costs. The model may therefore understate expected costs of bringing a biologic product to market and, thus, understate expected breakeven periods.³⁶

VIII. SOME FURTHER EXTENSIONS AND SENSITIVITY ANALYSIS OF THE NATURE MODEL

Data exclusivity periods should be established that are robust to alternative reasonable assumptions for contribution margin, cost of capital, biosimilar share, and brand price discounts in response to biosimilar entry. Brill relies on the following assumptions:

- Contribution margin of 60%
- Biotech cost of capital of 10%
- Biosimilar shares increasing from 10% in the first year to 35% by the fourth year of biosimilar entry
- Brand price discounts increasing from 20% in the first year to 40% by the fourth year of biosimilar entry.

This section presents the results of sensitivity analyses on a range of potential values for each of these key assumptions.

A. SENSITIVITY ANALYSES ON COST OF CAPITAL AND MARGIN ASSUMPTIONS

Table 2 presents the results of sensitivity analyses on breakeven period findings for different cost of capital and contribution margins, and also includes Brill's cost of capital and

³⁶ Alternatively, this approach is akin to assuming production is outsourced with a contract manufacturing charge equal to book depreciation charges. This also would be a conservative assumption since contractors would have to obtain a margin above depreciation costs to be a viable business.

data exclusivity assumption for comparison. The breakeven periods are reported for data exclusivity periods of 7 years, 10 years, 12 years, 14 years, and 16 years. The results reflect the same biosimilar share and brand price erosion assumptions that Brill uses (i.e., a biosimilar share of 10% in the first year of biosimilar entry, increasing to 35% by year 4, and a 20% brand price discount in the first year of biosimilar entry increasing to 40% by year 4, reflecting a branded competition model). Results indicate that a data exclusivity period of 12 to 16 years is required for breakeven periods of less than 50 years, under reasonable assumptions.

The cost of capital and margin assumptions applied in the sensitivity analyses include:

- The best current estimate now available of the cost of capital for the biotechnology industry is 13.25%, as supported by Golec and Vernon (2007). Breakeven periods are estimated under cost of capital assumptions including the 11.5% and 12.5% assumptions from the *Nature* article, Golec and Vernon's finding of 13.25%, and a real cost of capital estimate of 14.1% based on Ibbotson's median three-factor Fama-French measure. As stated, the 11.5% and 12.5% assumptions are lower than the best current estimates for cost of capital in the biotechnology industry, and therefore would have the effect of understating breakeven periods.
- A contribution margin of 50% is reasonable based on large successful biotechnology companies. Half of the companies in the sample of very successful biotechnology companies used by Brill earn contribution margins of 50% or less. Furthermore, small biotechnology companies typically have margins that are substantially lower. As a result, 50% likely overstates the margin that would be earned by an average biotechnology company. The sensitivity of findings is tested by applying average contribution margins of 60%, 55%, 50%, 45%, and 40%.

The cost of capital and contribution margin sensitivities are reported relying on the same biosimilar share and brand price erosion assumptions that Brill implements (his interpretation of the CBO's assumptions in its cost estimate of S. 1695). In addition, sensitivities with respect to alternative biosimilar share and brand price discount assumptions are also calculated in the next section.

In general, results confirm the importance of a substantial data exclusivity period to R&D returns. Notably, with an exclusivity period of 7 years, the *only* combination of assumptions that yields a breakeven point of less than 50 years is the one used by Brill (i.e., a cost of capital of 10% and a contribution margin of 50% or lower). Even with a 12-year exclusivity period, reasonable breakeven periods are possible only under the more extreme assumptions (e.g., if the best current estimate of the cost of capital of 13.25% is assumed, breakeven is achieved only when the contribution margin assumption is 60%, and breakeven is achieved at 17 years).

Exhibits 4(a), 4(b) and 4(c) present the results for cumulative net present value over time for selected data exclusivity periods, assuming costs of capital of 11.5%, 12.5% and 13.25%, respectively, and a 50% average contribution margin. Exhibit 4(a) shows that the cumulative net present value of returns to the innovator approaches a value just above zero when a cost of capital of 11.5% is assumed and a 12-year exclusivity period is applied. The innovator fails to break even if a cost of capital of 12.5% is assumed under either a 12- or 14-year data exclusivity period (Exhibit 4(b)), and if a 13.25% cost of capital is assumed, the innovator does not break even with a 12-, 14- or even a 16-year data exclusivity period (Exhibit 4(c)).

Exhibits 5(a), 5(b) and 5(c) present the same sensitivities as in Exhibit 4 but assume a 55% average contribution margin. With the higher assumed contribution margin, the innovator would be able to break even with a 12 year data exclusivity period but only if the cost of capital

is 11.5% or 12.5% (Exhibits 5(a) and (b)). In this regard, breakeven is achieved for the combination of a 12.5% cost of capital and 12 year data exclusivity period in approximately 17 years (Exhibit 5(b)). Assuming instead the preferred Golec Vernon-derived 13.25% cost of capital, the innovator breaks even only with a 16-year data exclusivity period, but fails to do so with shorter exclusivity periods of 12 and 14 years (Exhibit 5(c)).

B. SENSITIVITY ANALYSES TO ALTERNATIVE BIOSIMILAR SHARE AND BRAND PRICE EROSION ASSUMPTIONS

1. Biosimilar Share and Brand Price Erosion Assumptions

In this section, we report alternative assumptions on biosimilar share and brand price erosion reported in the literature. We calculate the impact of some alternative assumptions on breakeven results in a series of sensitivity analyses.³⁷ Before presenting these calculations, as background, it is useful to review the CBO report assumptions, together with other studies that have considered the competitive effects of biosimilar entry.

Table 3 shows the peak market penetration and biosimilar price discount estimates from four recent studies. Each of these studies is focused on established biologic products that could experience biosimilar competition over the next several years. Most studies generally acknowledge that biosimilar penetration rates are expected to increase as markets evolve from a regulatory, scientific, and reimbursement perspective. Hence, these estimates tend to underestimate penetration rates for the products which are now in discovery and development. Peak biosimilar penetration rates reflected in various recent studies range from 35 to 60%, with

³⁷ All of the assumptions in the sensitivity analyses are guided by the existing literature, economic theory, and the judgements of the authors.

the CBO estimate being the most moderate. Some of these figures reflect biosimilar penetration rates only among the largest selling products, however, while the CBO estimate is described as a sales-weighted average. All of the studies are based on comparators that may be imperfect predictors of the future biosimilar market.

Table 3 also displays the corresponding assumptions on biosimilar price discounts relative to the pre-biosimilar entry price of branded products. In this case, the CBO estimate is generally consistent with other sources at least in terms of initial year price discounts. All of the studies shown expect discount rates to reach at least 25 percent over time, especially for larger-selling products where more entrants are expected.

In terms of the branded products' competitive response to biosimilar entry, only one of the sources in Table 3, Avalere, provides an initial estimate of expected branded product's price impacts.³⁸ In general the Avalere study predicts that the reference brand will decrease prices in response to biosimilar entry.³⁹ Economic theory suggests that a competitive price response on the part of the innovator is expected, where there is a small number of entrants in these markets.⁴⁰

Given these considerations and possibilities, further sensitivity analyses appear warranted on biosimilar share and the brand's price response.

³⁸ Ahlstrom, A., et al., "Modeling Federal Cost Savings from Follow-On Biologics, White Paper, Avalere Health, April, 2007 <http://www.avalerehealth.net/research/docs/Modeling_Budgetary_Impact_of_FOBs.pdf>, accessed December 20, 2008.

³⁹ Avalere has indicated they are refining their estimates on branded share and price impacts as new information becomes available.

⁴⁰ Grabowski, H., Ridley, D., and Schulman, K., "Entry and Competition in Generic Biologics," *Managerial and Decision Economics*, 2007, 28(4-5), pp. 439-451.

2. Results of Sensitivity Analyses

Table 4 presents the breakeven period findings for alternative assumptions on biosimilar share and brand price erosion. Specifically, we test the following brand share and price erosion assumptions:

- **Biosimilar share** is assumed to be 10% in the first year of entry regardless of scenario, but we test alternative steady-state biosimilar shares in year 4 of 25%, 35%, 45%, and 55%. The 35% assumption is consistent with Brill's assumptions; other values are associated with other recent estimates shown in Table 3.
- **Brand price erosion** is assumed under three scenarios: to be 0% in all years (i.e., no increase or decrease in real brand prices from the point of biosimilar entry); to be a 10% brand price decrease in year 1, increasing to a steady-state decrease of 25% by year 4; or to be a 20% decrease in year 1, increasing to a steady-state decrease of 40% in year 4, relative to real prices at the point of biosimilar entry.⁴¹ The scenario that assumes brand price erosion increasing from 20% to 40% in the first four years is consistent with Brill's assumptions.

As shown in Table 4, a 10 year data exclusivity period is consistent with breakeven only in the extreme case where both the cost of capital and margin assumptions fall beyond the best baseline estimates.

All of the above described sensitivity analyses reflect a cost of capital of 13.25% and a contribution margin of 50%. The breakeven periods are reported for data exclusivity periods of

⁴¹ Since over time nominal prices for biologics are expected to be adjusted for inflation and other factors, reductions have been reflected on a real, or inflation-adjusted, basis in the *Nature* model. Assuming no real price changes implies nominal price will increase only with inflation.

7 years, 10 years, 12 years, 14 years, and 16 years. As in the earlier sensitivity analyses, the results for these brand share and price erosion sensitivity analyses suggest that limiting the data exclusivity period to less than 12 to 16 years results in failure of the representative portfolio of biologics to break even within an extended period of time, under reasonable assumptions.

As a further sensitivity analysis, Table 5 presents results for similar calculations as those presented in Table 4, but assuming a lower cost of capital of 12.5% and a higher contribution margin of 55%. The results in Table 5 are likely to understate breakeven periods as the cost of capital is lower than the best estimate for biotechnology investments and the contribution margin is higher than for many biotechnology companies. Nevertheless, data exclusivity periods of less than 12 to 16 years are still associated with long, or no, breakeven period. For data exclusivity periods of 7 years, breakeven periods of less than 50 years only occur with no brand price discounts and limited biosimilar shares. For data exclusivity periods of 10 years, breakeven periods of less than 20 years only occur with no brand price discounts; and breakeven periods of less than 50 years occur with moderate brand price discounts (10% to 25%) and limited biosimilar shares.

The analysis presented by Brill and the sensitivity analyses that are presented in this paper are based on worldwide revenues, and it should be noted that these worldwide revenues will be affected by variation in data or market exclusivity periods worldwide. In a review of top selling biologic drugs, the U.S. market is by far the most significant, varying substantially depending on where the drug is in its life cycle.⁴² As a result, because volume is a key driver,

⁴² According to a December 12, 2008 telephone call with a Sanford C. Bernstein & Co. analyst, in 2008, U.S. sales as a percentage of world-wide sales for all tracked biologic products are expected to average

U.S. data exclusivity periods are likely to have the most significant impact on biologic revenues and investor decisions.

IX. SUMMARY AND CONCLUSIONS

Identifying an appropriate data exclusivity period for biologics is an important component of any bill meant to establish an abbreviated regulatory pathway for biosimilar entry. The data exclusivity period is an essential component in allowing investors to earn a market return on biotechnology investments. As a result, continued investment in biotechnology research, and the valuable new products that such investment will produce, is dependent upon the establishment of an appropriate data exclusivity period in conjunction with any legislation establishing an abbreviated biosimilar regulatory approval pathway.

Appropriately modifying the Nature article breakeven model to consider the effects of biosimilar entry on market shares and prices indicates that limiting the data exclusivity period to less than 12 to 16 years results in failure of the representative portfolio of biologics to break even within an extended period, under reasonable assumptions. An adequate exclusivity period is necessary to maintain incentives to invest in the development of innovative new biologic products.

This finding is in stark contrast to the seven-year data exclusivity period suggested by Brill and others, and reflects the correction of errors in Brill's application of the model and the sensitivity of Brill's results to small changes in the key assumptions.

66%. Danzon and Furukawa (2006) previously report that U.S. biologics spending represented 63% of the ten countries examined in 2005.

As discussed in the earlier *Nature* article, analyses of breakeven lifetimes, based on historical cost and revenue data, are only one guidepost for selecting appropriate data exclusivity periods. The future environment for biologic innovation may differ from the past in many important ways – including the cost of development, prices and sales revenue, and the intensity of competition from branded therapeutic alternatives and from biosimilars. Nevertheless, a substantial data exclusivity period also appears to be consistent with a few core principles and facts that were outlined in that article and the introduction to this paper:

- Biologic introductions have been among the most novel therapies directed at life threatening and disabling diseases and offer hope for many important unmet medical needs for thousands of patients.
- There is currently a rich pipeline of product candidates in discovery and development from a spectrum of small start-up firms to larger established entities. Most of this pipeline emanates from firms without marketed products whose investors are very sensitive to expected future returns and risks, as many product candidates never make it to market, and there is no guarantee that those that do will be successful. Even for larger firms, the risk and investment associated with biologics research and development is large.
- The nature of patent protection for biologic products necessitates a strong complementary data exclusivity form of protection.

Given the tremendous potential benefits to patient from new biologics, setting a sufficient data exclusivity period to maintain investment incentives under a range of reasonable assumptions about expected returns should be an important consideration.

Appendix – A Note on Brill's Computational Inconsistencies

The sales and price erosion assumptions that Brill relies upon require three modifications to the model presented in the *Nature* article based on the time of biosimilar entry:

(1) Brand biologic revenues must be reduced based on the assumed brand price discount in response to biosimilar entry, and according to the time path of assumed price discounting. This adjustment reflects the fact that even if the same number of units of the brand product are sold, those sales generate less revenue due to the price discount.

(2) The assumed profit margin earned by the brand biologic must be adjusted to reflect the fact that brand price discount results in a smaller margin. Moreover, in computing margins one also expects costs to decline given changes in output and sales. It is reasonable to assume that production and other costs will decline in proportion to output reductions.

(3) Brand biologic revenues must be reduced by the assumed share of sales that the biosimilar is assumed to capture, and according to the time path of assumed biosimilar penetration. This adjustment reflects the fact that fewer units of the brand may be sold following biosimilar entry. Similarly, non-R&D production costs must be adjusted proportionately.

Brill makes the second and third of these modifications, but fails to implement the first. As a result, he overstates the level of brand biologic revenues following biosimilar entry that would be implied by his assumptions.

As an example for purposes of illustration, assume the following set of facts, and perform the associated calculations:

- Assume brand revenues in absence of biosimilar entry are \$1,000.
- Further assume that with biosimilar entry, the biosimilar captures 35% of unit sales and the brand reduces its price by 40%.
- Brand revenues for determining cash flow in the presence of biosimilar entry are then \$390, calculated as: $\$1,000 \times (1 - 35\%) \times (1 - 40\%) = \390 , to which one would then apply the appropriate profit margin. Assuming that after taking account of the price changes, the appropriate margin in this illustrative example of 50%, the total margin contribution would be \$195.

Brill's calculation error would instead yield the incorrect figure of \$650 in brand revenues, calculated as $\$1,000 \times (1 - 35\%)$, and \$325 in total margin contribution, again assuming a 50% margin.⁴³

⁴³ The margin is assumed to not be affected by the share penetration of the biosimilar; that is, the share of unit sales captured by the biosimilar is assumed to reduce costs and revenues proportionally. Conversely, the brand price decline is assumed to reduce revenues but not costs, resulting in a lower margin.

Table 1
Cost of Capital Estimates for the Biotechnology Industry

Source	Sector/Group	Model	Cost of Capital	
			Nominal	Real
Golec & Vernon (2007)	Biotech industry-wide	Fama-French	16.75%	13.25%
Ibbotson [1]	Median	Fama-French	17.49%	14.07%
Grossman (2003) [2]	Large drug companies	CAPM	15.70%	12.33%
	Biotech with ≥ 1 drug approved	CAPM	18.70%	15.24%
	Biotech drugs in phase II or III trials	CAPM	27.40%	23.69%
	Medium-sized publicly traded	CAPM	19%	14%
Myers and Shyam-Sunder (1995)	Small firms	CAPM		16%
Grabowski (2008) [3]	Biotech industry-wide	CAPM		11.5%-12.5%

Notes:

Highlighted cells indicate calculated estimates of real cost of capital based on reported nominal values and assuming a 3% annual inflation rate.

[1] The reported number is for the WACC; Ibbotson includes 73 firms in SIC 2836.

[2] Grossman (2003) relies on a nominal risk free rate of 6.8% and a risk premium of 8.6%.

[3] Grabowski (2008) estimates are based on DiMasi and Grabowski (2007).

Table 2
Breakeven Periods in Years

Alternative Cost of Capital and Contributions Margin Assumptions
Seven-and Ten-Year Data Exclusivity Periods

7-Year Data Exclusivity Period:

Cost of Capital	Contribution Margin				
	60%	55%	50%	45%	40%
	10%	13.5	>50	>50	>50
	11.5%	>50	>50	>50	>50
	12.5%	>50	>50	>50	>50
	13.25%	>50	>50	>50	>50
	14.1%	>50	>50	>50	>50

10-Year Data Exclusivity Period:

Cost of Capital	Contribution Margin				
	60%	55%	50%	45%	40%
	11.5%	10.6	14.5	>50	>50
	12.5%	17.4	>50	>50	>50
	13.25%	>50	>50	>50	>50
	14.1%	>50	>50	>50	>50

Sources:

- [1] Calculations based on the *Nature* model and Brill's interpretation of CBO assumptions for market share and price decline.
 [2] Real costs of capital:
 11.5% and 12.5% - Grabowski (2008)
 13.25% - Golec and Vernon (2007) and Vernon (2008)
 14.1% - Ibbotson median Fama-French WACC for SIC 2836, assuming 3% inflation.

Notes:

- [1] Cells highlighted in yellow reflect a breakeven period of under 50 years.
 [2] Cells highlighted in pink reflect no breakeven within a 50 year period.

Table 2 (Continued)
Breakeven Periods in Years

Alternative Cost of Capital and Contributions Margin Assumptions
Twelve-, Fourteen-, and Sixteen-Year Data Exclusivity Periods

12-Year Data Exclusivity Period:

Cost of Capital	Contribution Margin				
	60%	55%	50%	45%	40%
	11.5%	10.4	11.4	14.2	>50
	12.5%	11.9	17.3	>50	>50
	13.25%	17.1	>50	>50	>50
	14.1%	>50	>50	>50	>50

14-Year Data Exclusivity Period:

Cost of Capital	Contribution Margin				
	60%	55%	50%	45%	40%
	11.5%	10.4	11.4	12.9	>50
	12.5%	11.9	13.5	>50	>50
	13.25%	13.6	>50	>50	>50
	14.1%	>50	>50	>50	>50

16-Year Data Exclusivity Period:

Cost of Capital	Contribution Margin				
	60%	55%	50%	45%	40%
	11.5%	10.4	11.4	12.9	15.4
	12.5%	11.9	13.5	16.3	>50
	13.25%	13.6	16.4	>50	>50
	14.1%	18.9	>50	>50	>50

Sources:

[1] Calculations based on the *Nature* model and Brill's interpretation of CBO assumptions for market share and price decline.

[2] Real costs of capital:

11.5% and 12.5% - Grabowski (2008)

13.25% - Golec and Vernon (2007) and Vernon (2008)

14.1% - Ibbotson median Fama-French WACC for SIC 2836, assuming 3% inflation.

Notes:

[1] Cells highlighted in yellow reflect a breakeven period of under 50 years.

[2] Cells highlighted in pink reflect no breakeven within a 50 year period.

Table 3

**Biosimilar Assumptions
In Several Recent Studies**

Source [1]	Peak Biosimilar Penetration Rate	Basis	Biosimilar Price Discount (Relative to Pre-Entry Brand Price)
CBO (2008)	10% (year 1) to 35% (year 4)	Similar market situations	20% (year 1) to 40% (year 4)
Grabowski, et. al. (2007)	10 - 45%	Higher estimates correspond to complex small molecules	10% - 30% (year 1)
Express Scripts (2007)	49%	Therapeutic alternatives	25% (year 1)
Avalere Health (2007) [2]	60% ²	Average small molecule generic drug penetration rates	20% (year 1) to 51% (year 3)

Notes:

1. Congressional Budget Office, Cost Estimate: S.1695 Biologics Price Competition and Innovation Act of 2007, June 25, 2008.
Grabowski, H., Cockburn, I., Long, G. and Mortimer, R. "The Effect on Federal Spending of Legislation Creating a Regulatory Framework for Follow-on Biologics: Key Issues and Assumptions," Duke University, Department of Economics Working Paper, August, 2007.
Miller, S., and Houts, J., "Potential Savings of Biogenerics in the United States," whitepaper, Express Scripts, February 2007.
Ahlstrom, A., et al., "Modeling Federal Cost Savings from Follow-On Biologics," whitepaper, Avalere Health, April, 2007.
2. This estimate is for largest selling products. Avalere Health is conducting further analysis.

Table 4
Breakeven Periods in Years

Sensitivity of Findings to Price and Share Assumptions
13.25% Cost of Capital and 50% Contribution Margin

Brand Price Discount (Year 1 to Year 4 and beyond)				
	No Price Decline	10% year 1 to 25% year 4+	20% year 1 to 40% year 4+	
Biosimilar Share (year 4 and beyond)	7-Year Data Exclusivity Period:			
	25%	>50	>50	>50
	35%	>50	>50	>50
	45%	>50	>50	>50
	55%	>50	>50	>50
	10-Year Data Exclusivity Period:			
	25%	>50	>50	>50
	35%	>50	>50	>50
	45%	>50	>50	>50
	55%	>50	>50	>50
	12-Year Data Exclusivity Period:			
	25%	>50	>50	>50
	35%	>50	>50	>50
	45%	>50	>50	>50
	55%	>50	>50	>50
	14-Year Data Exclusivity Period:			
	25%	30.3	>50	>50
	35%	>50	>50	>50
	45%	>50	>50	>50
	55%	>50	>50	>50
	16-Year Data Exclusivity Period:			
	25%	25.9	>50	>50
	35%	28.7	>50	>50
	45%	37.7	>50	>50
	55%	>50	>50	>50

Sources:

- [1] Calculations based on the *Nature* model.
 [2] Real costs of capital 13.25% - Golec and Vernon (2007) and Vernon (2008)

Notes:

- [1] Cells highlighted in yellow reflect a breakeven period of under 50 years.
 [2] Cells highlighted in pink reflect no breakeven within a 50 year period.
 [3] Biosimilar share is assumed to be 10% in year 1 for all scenarios.

Table 5
Breakeven Periods in Years

Sensitivity of Findings to Price and Share Assumptions
12.5% Cost of Capital and 55% Contribution Margin

Biosimilar Share (year 4 and beyond)	Brand Price Discount (Year 1 to Year 4 and beyond)			
		No Price Decline	10% year 1 to 25% year 4+	20% year 1 to 40% year 4+
	7-Year Data Exclusivity Period:			
	25%	16.9	>50	>50
	35%	19.6	>50	>50
	45%	27.2	>50	>50
	55%	>50	>50	>50
	10-Year Data Exclusivity Period:			
	25%	14.5	20.7	>50
	35%	14.9	24.2	>50
	45%	15.5	42.7	>50
	55%	16.4	>50	>50
	12-Year Data Exclusivity Period:			
	25%	13.7	14.4	16.7
	35%	13.7	14.5	17.3
	45%	13.7	14.5	18.1
	55%	13.8	14.6	19.4
	14-Year Data Exclusivity Period:			
	25%	13.5	13.5	13.5
	35%	13.5	13.5	13.5
	45%	13.5	13.5	13.5
	55%	13.5	13.5	13.5
	16-Year Data Exclusivity Period:			
	25%	13.5	13.5	13.5
	35%	13.5	13.5	13.5
	45%	13.5	13.5	13.5
	55%	13.5	13.5	13.5

Sources:

- [1] Calculations based on the *Nature* model.
[2] Real costs of capital 12.5% - Grabowski (2008)

Notes:

- [1] Cells highlighted in yellow reflect a breakeven period of under 50 years.
[2] Cells highlighted in pink reflect no breakeven within a 50 year period.
[3] Biosimilar share is assumed to be 10% in year 1 for all scenarios.

Exhibit 1

Cumulative Net Present Value of Cash Flows for Representative Biotech Drug

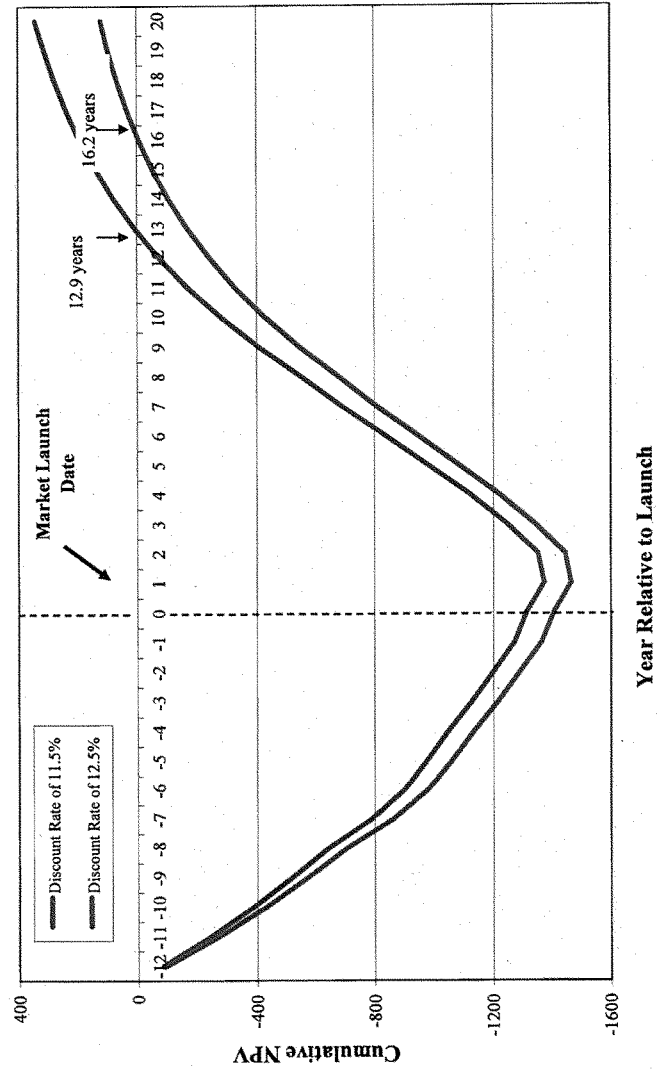
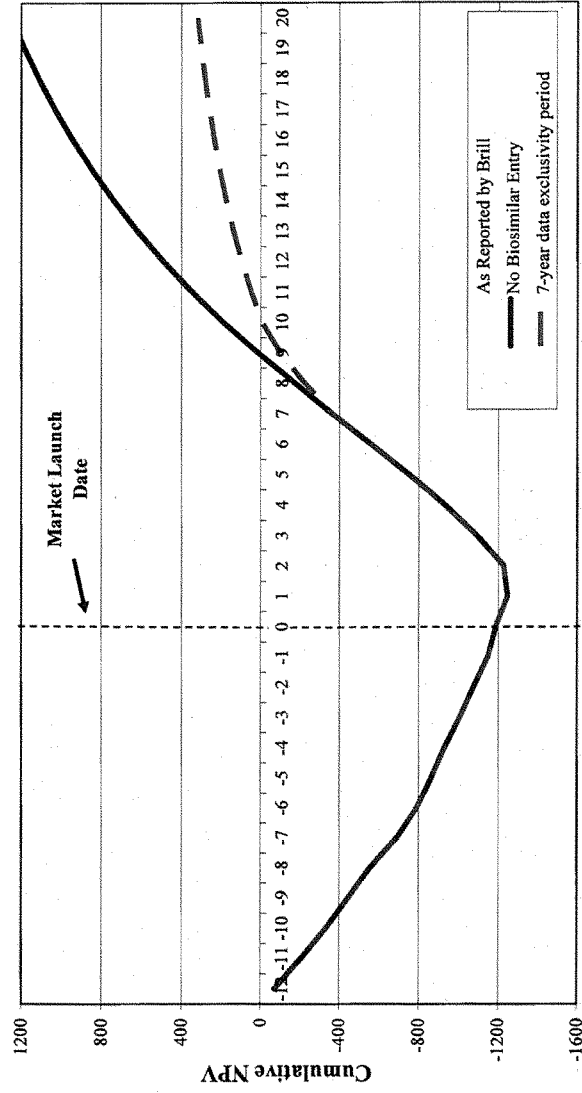


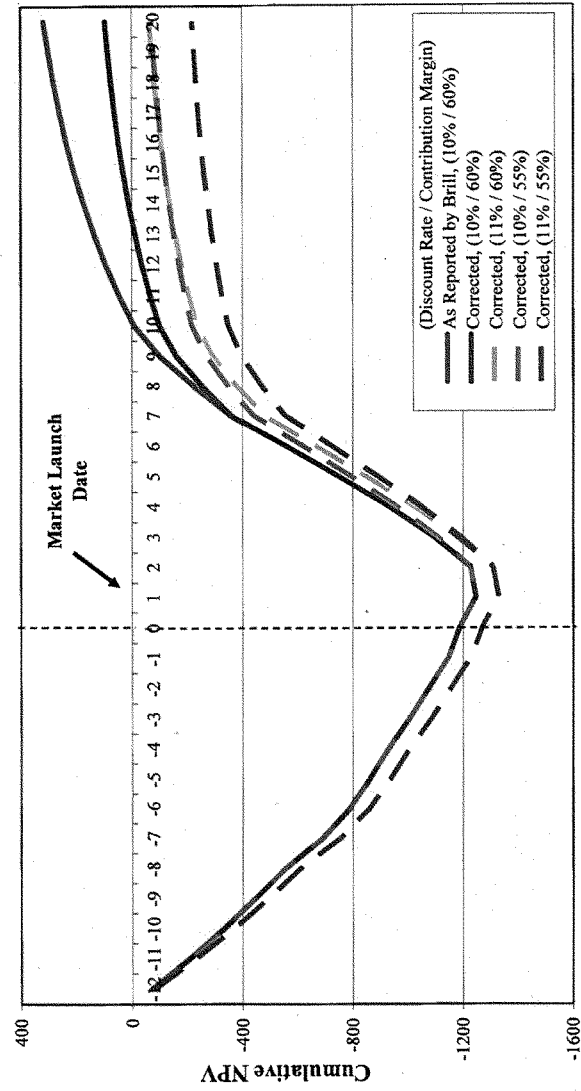
Exhibit 2
Cumulative Net Present Value of Cash Flows for Representative Biotech Drug
Brill Representation



Year Relative to Launch

Note: All scenarios maintain Brill's assumption of a 7-year data exclusivity period and biosimilar share and innovator price discounts, based on his interpretation of CBO share and price assumptions.

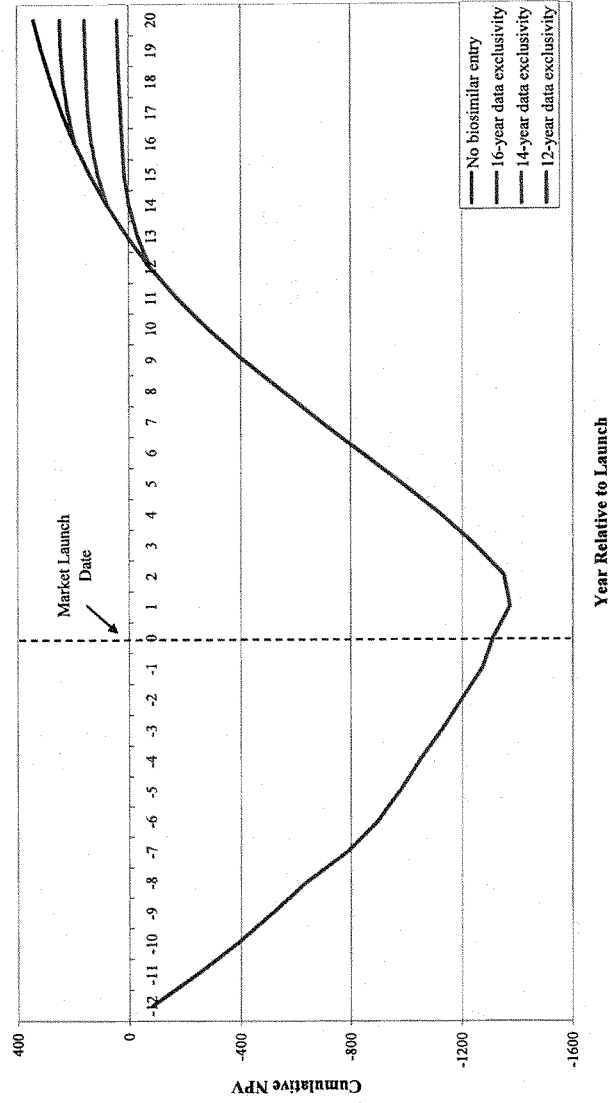
Exhibit 3
Cumulative Net Present Value of Cash Flows for Representative Biotech Drug
Brill Representation



Year Relative to Launch

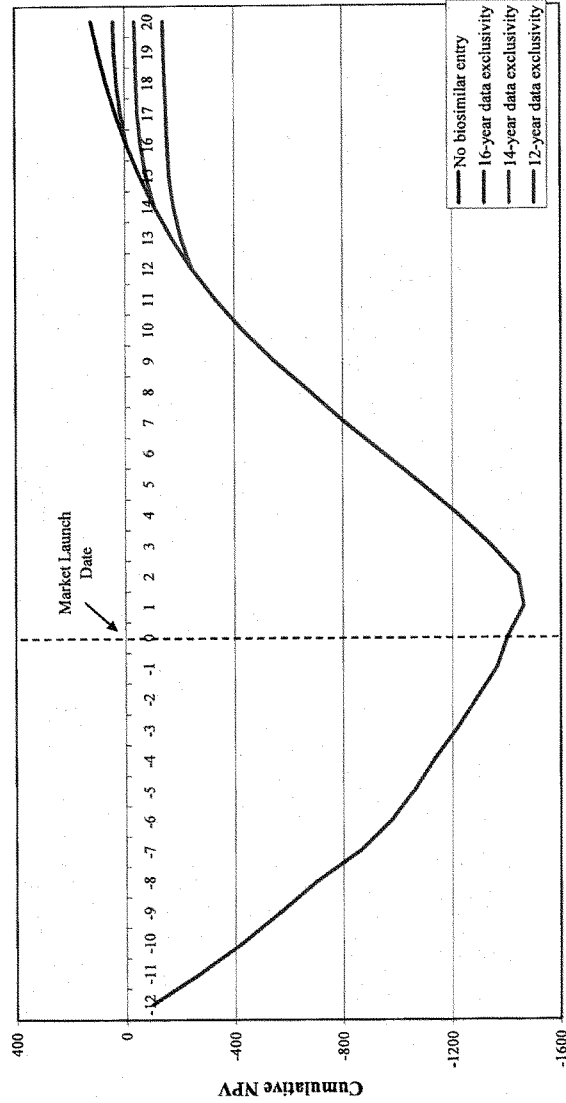
Note: All scenarios maintain Brill's assumption of a 7-year data exclusivity period and biosimilar share and innovator price discounts, based on his interpretation of CBO share and price assumptions. The innovator does not breakeven within 50 years with either an 11% discount rate, a 55% long-run contribution margin, or both.

Exhibit 4(a)
Sensitivity Analysis of Cumulative NPV of Cash Flows for Representative Biotech Drug
(50% Average Contribution Margin, 11.5% Cost of Capital)



Note: Biosimilar is assumed to capture 10% share in first year, increasing to 35% by year 4. Innovator price is assumed to decline 20% in first year of biosimilar entry, and 40% by year 4. Assumptions reflect Brill's interpretation of CBO assumptions.

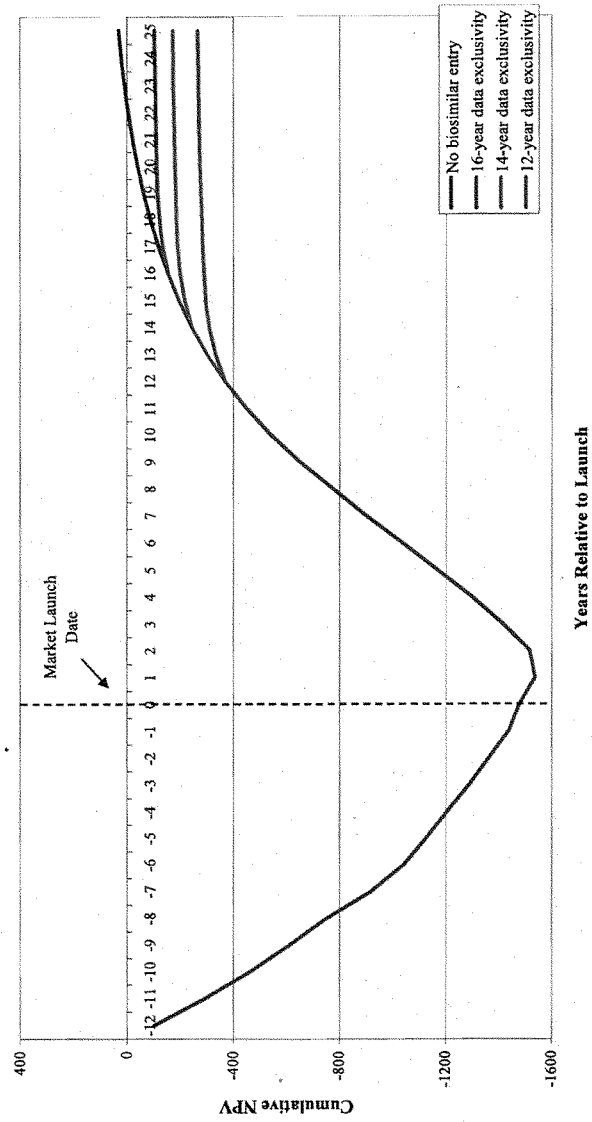
Exhibit 4(b)
Sensitivity Analysis of Cumulative NPV of Cash Flows for Representative Biotech Drug
(50% Average Contribution Margin, 12.5% Cost of Capital)



Years Relative to Launch

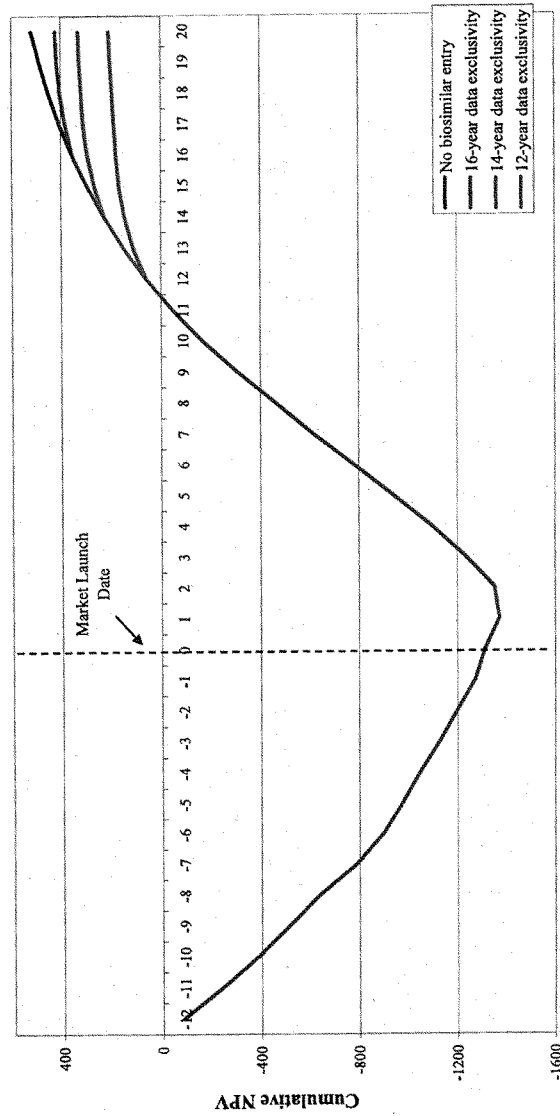
Note: Biosimilar is assumed to capture 10% share in first year, increasing to 35% by year 4. Innovator price is assumed to decline 20% in first year of biosimilar entry, and 40% by year 4. Assumptions reflect Brill's interpretation of CBO assumptions.

Exhibit 4(c)
Sensitivity Analysis of Cumulative NPV of Cash Flows for Representative Biotech Drug
(50% Average Contribution Margin, 13.25% Cost of Capital)



Note: Biosimilar is assumed to capture 10% share in first year, increasing to 35% by year 4. Innovator price is assumed to decline 20% in first year of biosimilar entry, and 40% by year 4. Assumptions reflect Brill's interpretation of CBO assumptions.

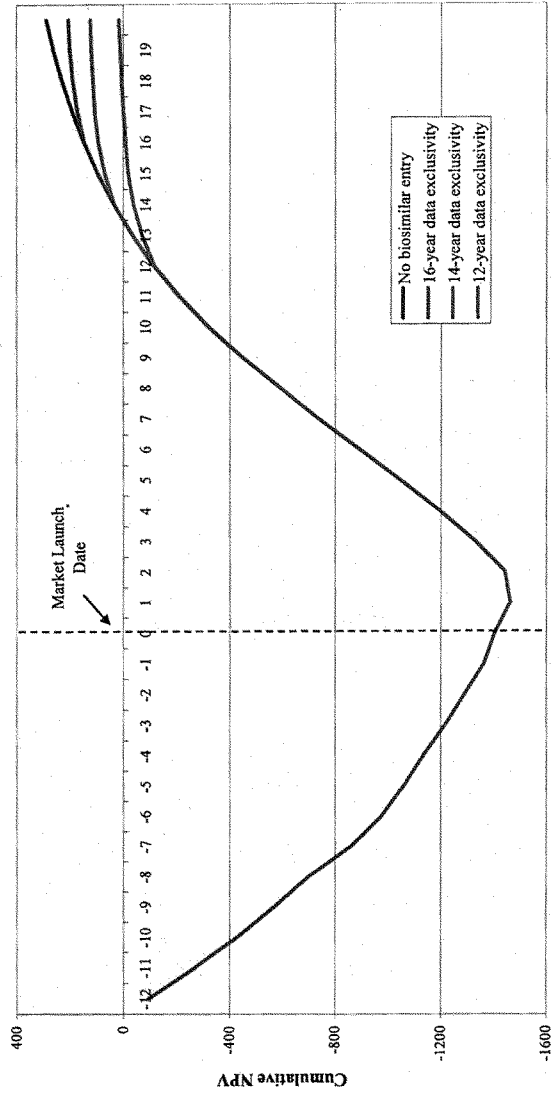
Exhibit 5(a)
Sensitivity Analysis of Cumulative NPV of Cash Flows for Representative Biotech Drug
(55% Average Contribution Margin, 11.5% Cost of Capital)



Years Relative to Launch

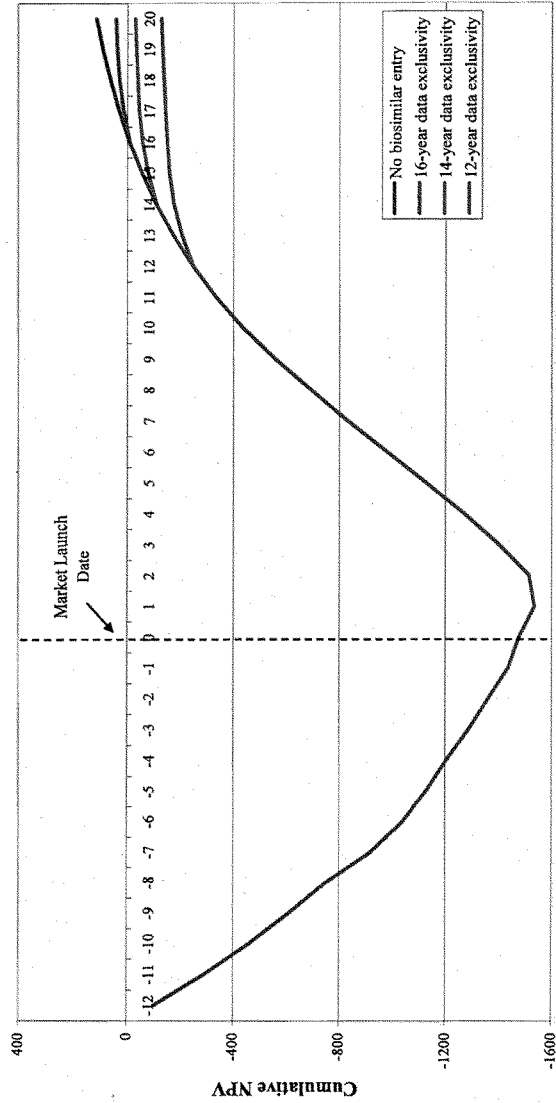
Note: Biosimilar is assumed to capture 10% share in first year, increasing to 35% by year 4. Innovator price is assumed to decline 20% in first year of biosimilar entry, and 40% by year 4. Assumptions reflect Brill's interpretation of CBO assumptions.

Exhibit 5(b)
Sensitivity Analysis of Cumulative NPV of Cash Flows for Representative Biotech Drug
(55% Average Contribution Margin, 12.5% Cost of Capital)



Note: Biosimilar is assumed to capture 10% share in first year, increasing to 35% by year 4. Innovator price is assumed to decline 20% in first year of biosimilar entry, and 40% by year 4. Assumptions reflect Brit's interpretation of CBO assumptions.

Exhibit 5(c)
Sensitivity Analysis of Cumulative NPV of Cash Flows for Representative Biotech Drug
(55% Average Contribution Margin, 13.25% Cost of Capital)



Note: Biosimilar is assumed to capture 10% share in first year, increasing to 35% by year 4. Innovator price is assumed to decline 20% in first year of biosimilar entry, and 40% by year 4. Assumptions reflect Brill's interpretation of CBO assumptions.



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

The Honorable Frank Pallone, Jr.
Chairman
Subcommittee on Health
Committee on Energy and Commerce
House of Representatives
Washington, D.C. 20515-6115

SEP 18 2008

Dear Mr. Chairman:

Thank you for your letter dated April 3, 2008, cosigned by Mr. Nathan Deal, Ranking Member, Subcommittee on Health, Committee on Energy and Commerce, regarding a pathway for follow-on biologic (FOB) products. We have restated each of your questions in bold below, followed by our response. Please note that there are several questions that FDA did not address as they do not fall within the Food and Drug Administration's (FDA or Agency) purview.

Science/Safety

1. **What is immunogenicity? Why is immunogenicity a special concern for biologics and what are the risks to patients? Do immunogenicity risks vary depending on the type of biologic?**

Immunogenicity is the ability to stimulate an immune response. An immune response to a therapeutic protein can range from development of detectable but not clinically significant antibodies to an immune response with significant impact on safety or effectiveness, including the potential to decrease or block the clinical effect of the therapeutic protein. Proteins are more likely to engender an immune response than smaller molecules. Adverse events secondary to immune responses can be life-threatening and include hypersensitivity reactions such as anaphylaxis, rash, fever and kidney problems, to cross-reaction with an endogenous protein (e.g., erythropoietin). Immune responses to administered protein products can be life-threatening. Immunogenicity may be influenced by patient-related, disease-related, or product-related factors.

2. **To what degree, if any, is immunogenicity testing necessary? Should immunogenicity testing be mandated by statute for all follow-on biologics (FOBs) or should the Food and Drug Administration (FDA) be given discretion to determine whether such studies, and what types of studies, are needed on a case-by-case basis?**

Page 2 – The Honorable Frank Pallone, Jr.

The ability to predict immunogenicity of a protein product, particularly of the more complex proteins, is limited. We believe that there are few, if any, circumstances that could be envisioned where assessment of immunogenicity would not be critical. Therefore, some degree of clinical assessment for a follow-on biologic's immunogenic potential will likely be needed. The extent of independent testing needed will depend on a variety of scientific factors such as the intended indication, whether the product is to be administered chronically, the overall assessment of the product's immunogenic potential, and whether there is the possibility of generating a cross-reaction with an important endogenous molecule. As noted above, immune responses to administered protein products can be extremely serious or life-threatening; therefore, this issue requires significant attention and will vary on a case-by-case basis. We believe that such studies must be mandated in statute, while allowing FDA the discretion to determine how much data are necessary for the assessment of immunogenicity.

3. **Has FDA exercised appropriately its discretion whether to require immunogenicity testing for manufacturing changes? Should immunogenicity testing for manufacturing changes be mandated by statute, or should FDA be given discretion to determine whether such testing is necessary?**

FDA believes it has exercised appropriately its discretion whether to require immunogenicity testing for manufacturing changes. As outlined in "FDA Guidance Concerning Demonstration of Comparability of Human Biological Products, Including Therapeutic Biotechnology-Derived Products," each manufacturing change and each product may present unique safety, identity, purity, and potency concerns; therefore, the necessary information required for manufacturing changes will vary for different products and for the manufacturing stage at which a change is implemented. Likewise, the International Conference on Harmonization Guidance (Guidance for Industry: Q5E comparability of Biotechnology/Biological Products Subject to Changes in their Manufacturing Process), notes that when possible adverse consequences of a manufacturing change cannot be excluded, the manufacturer should consider performing clinical studies, especially taking into account the characteristics of the product including the potential for immunogenic responses.

4. **Should FOB applicants have to provide evidence of similarity, safety, and effectiveness of each indication separately or can evidence for one indication be extrapolated to another?**

The manufacturer will need to provide information that justifies the safety and efficacy of their product for each of the requested indications. However, the extent of clinically-derived, *indication-specific* information needed to support the approval of a product for multiple indications will depend on a number of factors. These include how well the mechanism of action of the FOB is understood, how well delineated are the established benefits and toxicities in each of the clinical settings, and the relationship between the product's physiochemical characteristics and its clinical activity.

5. **Under the Food and Drug Administration Amendments Act of 2007, Congress established new authorities for FDA to enforce drug safety. How should the new post-market authorities enacted in this legislation be applied to FOBs? Are post-**

Page 3 – The Honorable Frank Pallone, Jr.

market studies always needed for FOBs? Are there situations in which FOB applicants will need to conduct post-market studies that are different from those that have been required and/or requested for the reference product?

The postmarketing authorities enacted under the Food and Drug Administration Amendments Act of 2007 should be applied to FOBs in a manner comparable to other drugs and biologics. The need for postmarketing studies will be dictated by the contents of the application – what is known and what is not known. There may well be circumstances under which FOB applicants will need to conduct postmarketing studies. This may depend on what has previously been elucidated about the marketed product or may stem from identifiable differences between the two products.

6. **Should non-interchangeable FOBs be required by statute to have different non-proprietary names from the reference product? What should the standard be for interchangeable FOBs? What are the advantages and disadvantages of requiring different non-proprietary names, including any affect on patient safety? What alternatives are available?**

FOBs also present issues with pharmacovigilance (for example, post-market surveillance and withdrawal based on class or specific product concerns). Currently, all products are assigned an International Non-Proprietary Name (INN). This is highly relevant in the context of biosimilars, given that these products would be considered similar, rather than the same. FDA recognizes the complexity of developing a policy on non-proprietary naming of FOB products. Any such policy will need to consider potential impacts on the non-proprietary names of products currently on the market. FDA believes that legislation should recognize the potential impact on pharmacovigilance and prescribing and require that these products be assigned a distinguishable, non-proprietary name for safety purposes. FDA's paramount concern is that patients not be exposed to an avoidable safety risk by being switched to a product not known to be interchangeable with the product they are currently receiving.

7. **Is it important that an innovator and an FOB have the same mechanism of action? Why or why not? If the mechanism of action of the reference product is unknown, should the FOB applicant be required to determine the mechanism of action and ensure that both products share the same one? Why or why not?**

It is imperative that the reference product and the FOB have the same mechanism of action. In the case where the mechanism of action of the reference product is unknown, there will be greater uncertainty regarding the potential clinical significance of any structural differences between the reference product and the FOB. Any such uncertainty may need to be resolved via clinical studies. If the mechanism of action is known to be different, then the product cannot be considered to be a FOB.

8. **How much variability in chemical structure is there in individual brand biologics: (1) batch-to-batch, and (2) as a result of manufacturing changes? What are the implications, if any, for FOBs testing requirements, naming, and interchangeability?**

Page 4 – The Honorable Frank Pallone, Jr.

For individual brand protein products, the degree of variability in chemical structure from batch to batch or as a result of a manufacturing change depends on many factors, including the following: 1) the complexity of the product in terms of higher order folded structures and post translational modifications (e.g., glycosylations), as well as number of active components in the product; 2) the demonstrated robustness of the product's performance to structural variations; and 3) the impact of the manufacturing change on structural variability (e.g., the change may decrease variability). It is not possible to provide a single measure of variability that would be representative for all protein products.

With respect to interchangeability, a key aspect of generic drugs is that their chemical composition is the same as the innovator drug. Products approved under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), i.e., generic drugs, may be designated as therapeutically equivalent to the reference product, and thus considered "substitutable" or "interchangeable." Under State law, such products may be substituted for the reference product by a pharmacist, which may provide for cost savings.

However, protein products are more complex and are frequently immunogenic. The impact of immunogenicity can be serious and life threatening. In most cases, follow-on protein products will not be the same as the reference product in the manner that generic drugs approved under section 505(j) of the FD&C Act are the same as the listed drug. In addition, even if a follow-on protein product is determined to be biosimilar to the reference product, immunogenicity could preclude patients from switching from one product to another.

Because of the variability and complexity of protein molecules, current limitations of analytical methods, and the difficulties in manufacturing a consistent product, it is unlikely that, for most proteins, a manufacturer of a follow-on protein product could demonstrate that its product is identical to an already approved product. Technology is not yet sufficiently advanced to allow this type of comparison for more complex protein products. Scientific and safety issues of determining interchangeability at present are significant, including for pharmacovigilance (for example, postmarket surveillance and withdrawal based on class or a specific product).

For many follow-on protein products, there is a known significant risk in repeatedly switching between products and a resulting negative impact on both patient safety and/or effectiveness. Pharmacies or patients might substitute biological products determined to be biosimilar, but not determined to be interchangeable for one another, possibly resulting in serious injury or death. Therefore, while there may be the possibility of determining interchangeability in the future, in light of the current scientific limitations on the ability to make determinations of interchangeability, and because it is critical to protect patient safety, the Agency believes that patients should not be switched from the innovator biological product to a follow-on biological product (or vice versa) without the express consent and advice of the patient's physician.

As noted in the response to question 6, above, any policy on non-proprietary naming of follow-on protein products will need to consider potential impacts on the non-proprietary names of products currently on the market.

- 9. Should human clinical trials be mandated by statute for all FOBs or should FDA be given discretion whether such trials are needed on a case-by-case basis? Would not requiring human clinical studies of FOBs result in these products having a more difficult time reaching market acceptance? Why or why not?**

Applicants submitting a Biologics License Application (BLA) under section 351 of the Public Health Service Act (PHSA) are generally required to perform one or more clinical studies to establish that a biological product is safe, pure, and potent. FDA believes that legislation should require that sponsors of follow-on products meet the same high standards for approval as reference biological products. In order to meet this standard, the data needed to demonstrate that a product is safe, pure, and potent will depend, among other things, on the specific biological product at issue. For instance, the extent of clinical information required depends on how much is known regarding mechanism of action, degree to which structural similarity could be assessed, comparative pharmacokinetic and pharmacodynamic data, and immunogenicity. Given the current level of understanding, at least some clinical information will be needed to assess the safety and efficacy of most FOBs. Legislation should require clinical trials, but FDA should be given discretion to determine through a transparent and public process what clinical trials are needed to support the licensure of a FOB.

- 10. What studies have been required for past approvals of protein products under section 505 of the Federal Food, Drug, and Cosmetic Act (FFDCA)? Have any been approved without clinical trials?**

In general, the amount and type of new clinical (human) data required for approval of a follow-on protein product will be influenced by the extent to which the follow-on product can be demonstrated to be sufficiently similar to an approved protein product to permit some degree of reliance on the findings of safety and effectiveness for the approved product. For example, the approval of Omnitrope, a recombinant human growth hormone, in 2006 was based on comparative physicochemical, bioactivity, pharmacokinetic, pharmacodynamic, and clinical data (including immunogenicity data) demonstrating, with bridging across drug substance and formulation changes, that Omnitrope is highly similar to Genotropin, a previously approved recombinant human growth hormone. Although Omnitrope was approved in part in reliance upon FDA's finding of safety and effectiveness for Genotropin, Omnitrope has not been determined to be therapeutically equivalent to, and thus substitutable for, Genotropin.

We also have approved small (e.g., eight amino acid) synthetic peptide products under the abbreviated new drug application pathway at section 505(j) of the FD&C Act without clinical safety or effectiveness data.

At this time, we have not approved a recombinant protein (as distinguished from a synthetic or naturally-sourced protein) through the 505(b)(2) pathway without clinical trials (other than bioavailability or bioequivalence).

11. Omnitrope is approved in the U.S. (albeit as a 505(b)(2)) and in Europe (as the first biosimilar).

a. Have patients experienced any problems?

FDA's Center for Drug and Evaluation Research (CDER) conducted a search of the Adverse Event Reporting System (AERS) database through April 22, 2008, and identified two reports of adverse events submitted with regard to Omnitrope. Both were foreign reports. One report involved a 12-year-old boy with a history of growth hormone deficiency who experienced snoring and adenoidal hypertrophy (enlarged adenoids) two weeks after starting Omnitrope. The other report involved a 9-year-old girl with a history of Turner's syndrome who experienced thrombocytopenic purpura (a bleeding disorder characterized by low platelet count) about three years after starting Omnitrope. Based on these two reports in AERS, we cannot make any conclusion regarding Omnitrope-related adverse events.

b. Have patients been switched to Omnitrope from other recombinant human growth hormone products?

FDA has not determined that Omnitrope is therapeutically equivalent to, and thus substitutable for, any other sponsor's recombinant human growth hormone product. It is possible, however, that patients could be switched between recombinant human growth hormone products by a physician or other health care provider. Omnitrope is not therapeutically equivalent to any other human growth hormones but it is an alternative treatment option. CDER examined total dispensed prescriptions (new and refilled) for somatropin products using Verispan, LLC: Vector One®: Prescription Services (VONA/VOMA) for year 2007. These estimates do not include products dispensed from home health care pharmacies, which represents roughly a third of the wholesale distribution for somatropin. Presently, FDA does not have access to databases that can provide an estimate of dispensed prescriptions from these channels. The following information was noted as a result of database queries:

- In 2007, 195,501 new and refilled prescriptions for somatropin products were dispensed from retail and mail order pharmacies in the U.S. Omnitrope represents less than 1 percent of the somatropin market share for dispensed prescriptions.
- In 2007, an estimated 1,565 new and refilled prescriptions for Omnitrope were dispensed by retail and mail order pharmacies. Of these, less than 5 percent (69/1,565) of prescriptions were from patients who had previously received another Anabolic Hormone prescription within the previous 6 months AND also had a different brand dispensed in the same defined class of Anabolic Hormone for the past 6 months (switch/add-on activity¹). Of new Omnitrope prescriptions dispensed, when a patient was either switched to Omnitrope or when Omnitrope was added to the patient's current

¹ Switch activity is when the patient is switched from one brand of the drug to another. Add-on activity is when a patient remains on one brand while therapy with another brand is added.

Page 7 – The Honorable Frank Pallone, Jr.

therapy, around 78 percent (35/45) of the previously used products were other somatropin products.

- c. If the answer to part b is yes, how are payers handling the availability of this comparable product?**

FDA does not have access to information on how payers are handling the availability of Omnitrope.

Regulatory/Administrative

- 1. Some believe Section 505 of the FFDCA provides a regulatory pathway for approval of biosimilars for reference products approved under Section 505. Should a newly created biosimilar regulatory approval process include all biologics approved under the FFDCA as well as those regulated under the Public Health Service Act?**

FDA has approved some follow-on protein products under section 505(b)(2) of the FD&C Act. However, this is only for protein products where the innovator products are regulated and were approved as drugs under section 505 of the FD&C Act. The majority of protein products have been licensed as biological products under the PHSA. Currently, the PHSA does not contain an abbreviated approval pathway for biological products licensed under the PHSA that is analogous to the abbreviated approval pathways under sections 505(b)(2) or section 505(j) of the FD&C Act.

We believe that any proposal to transfer certain products now regulated under section 505 of the FD&C Act to section 351 of the PHSA should not be undertaken without very careful consideration of the legal and policy implications of such a change on the regulation of these products. For example, insulin products are proteins that have been regulated under the FD&C Act for more than 60 years. There could be significant regulatory implications if this product class were now to be approved or licensed and regulated under the PHSA. The Agency has not completed its considerations of this issue and would want to fully consider the potential implications of any specific proposal.

- 2. The current statute gives FDA discretion to decide whether a change in an approved biologic requires assessment through a clinical trial. Do you think this statutory discretion has been appropriate or adequate? What has been its effect on patient safety?**

FDA believes that the current statute that gives FDA discretion to decide whether a change in an approved biologic requires assessment through a clinical trial is adequate and appropriate.

- 3. What FDA office should review FOBs?**

Follow-on protein products will be reviewed by the same office in which the original approved product (the reference product) was reviewed.

4. **What standards are required to assure sufficient similarity between the FOB and the reference product? Is the requirement that the FOB be “highly similar” to the reference adequate or should an applicant be required to establish that the FOB is “as similar as scientifically as possible”? How would FDA assess these requirements?**

FDA believes that product-class guidances should be developed to outline what would be considered to be “highly similar” for the purposes of that specific class of products. This would ensure that FDA receives expert and public scientific and technical advice, but should include flexibility for FDA to adjust the process to meet its scientific needs with respect to data requirements and other matters. This guidance process would signal to stakeholders which product classes FDA considers appropriate for follow-on applications and data elements that might allow review and approval of a follow-on product. Such a process will ensure the Agency has optimum information regarding safety and efficacy considerations for follow-on products; enhance transparency of decision-making; establish a level-playing field for all follow-on applicants; and encourage follow-on applications by describing Agency expectations for application content.

5. **Should FDA be required to promulgate regulations and guidance before reviewing applications? Why or why not? Furthermore, should FDA be required to issue and permit public comment on product-specific guidance before submission of applications? What are the advantages and disadvantages? How long will it take to put a regulatory framework in place, including new regulations and guidances for FOBs?**

FDA believes that requiring a predictable and public product-class guidance process prior to acting on any follow-on applications would be beneficial. This process should ensure that FDA receives expert and public scientific and technical advice, but should include flexibility for FDA to adjust the process to meet its scientific needs with respect to data requirements and other matters. This guidance process would signal to stakeholders which product classes FDA considers appropriate for follow-on applications and data elements that might allow review and approval of a follow-on product. Such a process will ensure the Agency has optimum information regarding safety and efficacy considerations for follow-on protein products; enhance transparency of decision-making; establish a level-playing field for all follow-on applicants; and encourage follow-on applications by describing Agency expectations for application content.

The timeframe within which a regulatory framework, including new regulations and guidances for FOBs, could be established would depend upon the requirements of enacted legislation, the complexity of the product class, the volume of comments received through a public process, and the availability of Agency resources.

6. **How much in additional appropriations or user fees would FDA need to implement a generic biologics program? What proportion of resources should come from user fees? How would that relate to the user fees that are assessed for traditional drugs and/or biologics?**

Page 9 – The Honorable Frank Pallone, Jr.

To review follow-on applications, FDA will need additional resources. Although FDA has not yet had the opportunity to consider the full costs likely to be associated with the review of follow-on applications, FDA believes that these applications will require approximately the same resources initially as comparable BLAs and NDAs. In addition, there will be “start up” resources needed to launch the program.

In addition, in light of the importance of ensuring the timely review of safe and effective generic drugs, the Agency believes it is vital to authorize the collection of user fees for review of generic drug applications under section 505(j) of the FD&C Act consistent with the President's FY2009 budget.

Interchangeability

- 1. Does current science permit an assessment of interchangeability (substitutability) for any biologics at this time? What is the likelihood that interchangeability assessments for some or all biologics will be possible in the future, and in what period?**

Because of the variability and complexity of protein molecules, current limitations of analytical methods, and the difficulties in manufacturing a consistent product, it is unlikely that, for most proteins, a manufacturer of a follow-on protein product could demonstrate that its product is identical to an already approved product. Technology is not yet sufficiently advanced to allow this type of comparison for more complex protein products. Scientific and safety issues of determining interchangeability at present are significant, including for pharmacovigilance (for example, postmarket surveillance and withdrawal based on class or a specific product).

To establish that two protein products would be therapeutically equivalent (interchangeable), a sponsor of the follow-on protein product would need to demonstrate, among other things that repeated switches from the follow-on protein product to the referenced product, and vice versa, would have no negative effect on the safety and effectiveness of the products. It is likely that the manufacturer of a follow-on protein product would have to conduct clinical studies evaluating such switching before a claim of interchangeability would be permitted. The design and ethical considerations for such studies will require careful consideration. In light of the current scientific limitations on the ability to make determinations of interchangeability, and because it is critical to protect patient safety, FDA believes that patients should not be switched from the reference biological product to a follow-on biological product (or vice versa) unless directed to do so by their physician, and legislation should not allow for determinations of interchangeability at this time.

- 2. In general terms, what types of testing or data would be necessary to establish that two biologics are interchangeable?**

In general, demonstration of interchangeability would be based on, among other things, a showing of similar relevant structural characteristics between the two products, an understanding of the structure-function relationships, and clinical data evaluating the impact

of switching patients from one product to the other. There may be a need for standards to ensure structural similarity and interchangeability over the products' lifetime.

- 3. How should product-specific requirements for demonstrating interchangeability be established? Should the statute prohibit interchangeability assessments or give FDA the authority to determine interchangeability as science permits? Please explain your answer?**

As previously discussed, there is a known significant risk in repeatedly switching between products and a resulting negative impact on both patient safety and/or effectiveness. While there may be the possibility of determining interchangeability in the future, pharmacies or patients might substitute biological products determined to be biosimilar, but not determined to be interchangeable for one another, possibly resulting in serious injury or death. Therefore, in light of the current scientific limitations on the ability to make determinations of interchangeability, and because it is critical to protect patient safety, the Agency believes that patients should not be switched from the innovator biological product to a follow-on biological product (or vice versa) without the express consent and advice of the patient's physician, and legislation should not allow for determinations of interchangeability at this time.

- 4. Should there be product specific guidances, with opportunity for public comments, on establishing interchangeability before submission of applications? What are the advantages and disadvantages?**

As noted in the response to question number 5 under the Regulatory/Administrative section, above, FDA believes that the implementation of a public product-class guidance process prior to acting on any follow-on applications would be beneficial.

- 5. What are the potential risks to patients from interchangeability of one biologic for another? If FDA finds two biologics interchangeable, should physicians, pharmacists, and patients feel comfortable with substitution by pharmacist? Why or why not? How would interchangeability affect patient access to biologics?**

As noted in the response to question number 1 under the Science/Safety section, above, an immune response to a therapeutic protein can range from development of detectable but not clinically significant antibodies to an immune response with impact on safety or effectiveness. Adverse events from an immune response could include hypersensitivity reactions such as anaphylaxis, rash, fever and kidney problems, to cross-reaction with an endogenous protein (e.g., erythropoietin). Immune responses to administered protein products can be life-threatening. Immunogenicity may be influenced by patient-related, disease-related, or product-related factors. Thus, without clinical evidence that patients can be switched back and forth between two products without any detrimental effect, such changes should not be made unless directed by a physician, and legislation should not allow for determinations of interchangeability at this time.

Page 11 – The Honorable Frank Pallone, Jr.

6. How would interchangeability affect competition in the market place, and/or reimbursement by health plans? Will it affect the costs of biopharmaceuticals?

We believe that the complexity of the interchangeability issue would preclude reliance on a paradigm analogous to the generic drug model. We cannot speculate about the impact on pricing or health plans.

Patents

- 1. In your view, how long is the current effective patent term for pharmaceuticals? Specifically, how long on average are drugs marketed under patent protection following FDA approval?**
- 2. The Hatch/Waxman Act restored innovator patents up to 14 years, and further provided manufacturers with 5 years of data exclusivity. Is this a good model for biologic manufacturers? What lessons can we learn from the Hatch-Waxman Act, and apply towards Congress's discussion about FOBs?**

The patent term restoration provisions of the Hatch-Waxman Act, which restore up to 5 years of the term of an unexpired patent but which cannot result in a patent term longer than 14 years from the date of product approval, currently apply to biological products licensed under the PHSA (see 35 U.S.C. 156). The statute addresses, among other things, "a patent which claims a method of manufacturing the product which primarily uses recombinant DNA technology in the manufacture of the product..." (35 U.S.C. 156(a)(5)(B)). However, the 5-year exclusivity provision of the Hatch-Waxman Act applies only to drug products approved under section 505(b) of the FD&C Act (see section 505(c)(3)(E)(ii) of the FD&C Act).

The lessons learned from the Hatch-Waxman Act lead the Agency to believe that, to ensure continued innovation, legislation authorizing a follow-on biological pathway should include incentives to develop innovative biologic products. The Agency believes that sponsors that develop innovative biotechnology products should be eligible for a significant period of market and/or data exclusivity, independent from any patent protections that might be applicable to the product, to ensure continued innovation. An additional exclusivity period should also be provided if, during the period of exclusivity, the sponsor of the reference product submits, and FDA approves a BLA supplement for a new indication for which new clinical studies were required (other than bioavailability studies). Such protections should be robust enough to ensure that a follow-on pathway does not negatively impact innovation.

- 3. Please explain if patent on biotech medicines will provide meaningful protection of intellectual property if a pathway is created to allow for the regulatory approval of FOBs? How do patents on biotechnological medicines compare or differ in the value they offer to traditional small-molecule drugs, if an FOB's pathway requires only that the FOB be highly similar to the reference product?**

FDA's role in administering the patent listing provisions of the Hatch-Waxman Act and ensuring compliance with patent certification requirements is purely ministerial.

4. **What procedures, if any, should be included in legislation to enable reference product companies or third parties to identify potential patent infringement claims by a biosimilar company and to ensure timely resolution of legal disputes?**

The Agency does not have a position on the procedures that should be included in legislation to enable reference product companies or third parties to identify potential patent infringement claims related to FOBs. We note, however, that even FDA's limited current role in administering the patent listing provisions of the Hatch-Waxman Act and ensuring compliance with the patent certification requirements can embroil the Agency in litigation. The Agency believes that sponsors that develop innovative biotechnology products should be eligible for a significant period of market and/or data exclusivity, independent from any patent protections that might be applicable to the product, to ensure continued innovation.

5. **If patent issues are to be addressed in a statute, how should we balance the interests of third-party patent holders and the reference product sponsor?**
6. **Should an FOB statute require FDA to administer patent listing and notification provisions as Hatch-Waxman does? Has this process been an appropriate and efficient use of FDA's resources and expertise? Why or why not? Can appropriate notification be accomplished through an alternative process that does not enlist FDA resources?**

As stated in the response to question 4 above, the Agency does not have a position regarding whether the Hatch-Waxman patent listing and notification process would be appropriate for an FOB statute.

Incentives/Exclusivity/Investment

1. **Should reference product manufacturers be given a period of exclusive marketing in addition to the patent-term restoration already provided to them under Hatch-Waxman? If yes, how much is necessary to provide adequate incentives for innovation without unnecessarily delaying competition?**

The Agency believes that sponsors that develop innovative biotechnology products should be eligible for a significant period of market and/or data exclusivity, independent from any patent protections that might be applicable to the product, to ensure continued innovation. An additional exclusivity period should also be provided if, during the period of exclusivity, the sponsor of the reference product submits, and FDA approves, a BLA supplement for a new indication for which new clinical studies were required (other than bioavailability studies).

Such protections should be robust enough to ensure that a follow-on pathway does not negatively impact innovation.

Page 13 – The Honorable Frank Pallone, Jr.

2. **What types of assessments have been conducted to determine the minimum term of exclusivity that will enable a robust industry for discovery and development of biologics?**

3. **How should exclusivity for modifications to approved products be addressed?**

An additional exclusivity period should be provided if, during the period of exclusivity, the sponsor of the reference product submits and FDA approves, a BLA supplement for a new indication for which new clinical studies were required (other than bioavailability studies).

4. **What benefits do innovator firms obtain from data exclusivity, and how is this protection different from patent protection?**

A clearly-defined period of exclusivity provides certainty to reference product sponsors. Patent protection differs in that patents may be challenged by a follow-on protein product sponsor as invalid, unenforceable, and/or not infringed.

5. **Do you think biologics should receive a different period of data exclusivity than drugs?**

The Agency believes that sponsors that develop innovative biotechnology products should be eligible for a significant period of exclusivity protection to ensure continued innovation.

6. **What policy considerations justify that patent protections be the principal form of intellectual property for biologics and drugs?**

7. **If a follow-on biologics pathway was created without additional incentives – beyond existing patent protections – for continued innovation, how would innovation be affected either positively or negatively? What additional incentives, if any, would be necessary to support continued research and innovation, including at American universities?**

Innovation would be negatively affected by the creation of a follow-on biologics pathway without additional incentives beyond existing patent protections. Not all biologics are protected by a patent, and even if there is a patent the cost of litigating patent issues are significant. The cost of establishing that an original biologic product is safe and effective is high. Because a sponsor who developed the innovative biologic may not be able to obtain funding to do the necessary research if they cannot expect to recover the cost if the biologic is approved, additional incentives should be provided to encourage research into the safety and efficacy of biologics. The Agency believes that sponsors that develop innovative biotechnology products should be eligible for a significant period of market and/or data exclusivity, independent from any patent protections that might be applicable to the product, to ensure continued innovation. An additional exclusivity period should also be provided if, during the period of exclusivity, the sponsor of the reference product submits, and FDA approves a BLA supplement for a new indication for which new clinical studies were required

Page 14 – The Honorable Frank Pallone, Jr.

(other than bioavailability studies). Such protections should be robust enough to ensure that a follow-on pathway does not negatively impact innovation.

Economic Impact

1. **How much savings would a generic biologics pathway create and in what period (taking into account the time it will take to implement any new law, and the time needed by manufacturers to develop products and submit applications)? Please describe the evidence on which you base your answer.**
2. **Can you provide an estimate of the amount of money your agency/company will spend on biological products over the next 10 years, in absolute dollars, and as a percentage of total program/plan spending? If FOBs, approved by FDA as comparable to the brand name product, were available, what is your estimate for the cost of the reference product and the follow-on product?**
3. **What implications would a follow-on biologics pathway have on U.S. economic competitiveness and leadership in protection of intellectual property rights?**
4. **What implications does the treatment of patents in the context of a follow-on biologics approval pathway have for the future of biotechnological innovation?**

In general, a FOBs approval pathway may be expected to reduce the barrier to market entry for a follow-on product once a patent that claims the reference product expires. However, it is difficult to evaluate the implications of the treatment of patents in the context of a follow-on biological approval pathway outside of the context of other incentives for biotechnological innovation such as exclusivity protection, which may be coextensive with a significant portion of the term of a patent that claims the reference product.

5. **If a follow-on biologics pathway was created without ample incentives for innovators to continue to innovate, what would the effect be for future research, current clinical programs, and universities?**

The Agency believes that sponsors that develop innovative biotechnology products should be eligible for a significant period of exclusivity protection, independent from any patent protections that might be applicable to the product, to ensure continued innovation.

European Model (abbreviated approval pathway)

1. **The European Union (EU) regulatory system for biosimilars requires the development of product-specific guidances which detail the standard for approval that would need to be met by a biosimilar in a defined product class. Do you think these guidances would provide similar benefits to industry, healthcare providers, and patients in the U.S.?**

Page 15 – The Honorable Frank Pallone, Jr.

The Agency believes that a predictable and public product-class guidance process should be required prior to acting on any follow-on applications. It should ensure that FDA receives expert and public scientific and technical advice, but should include flexibility for FDA to adjust the process to meet its scientific needs with respect to data requirements and other matters. This guidance process would signal to stakeholders which product classes FDA considers appropriate for follow-on applications and data elements that might allow review and approval of a follow-on product. Such a process will ensure the Agency has optimum information regarding safety and efficacy considerations for follow-on products; enhance transparency of decision-making; establish a level-playing field for all follow-on applicants; and encourage follow-on applications by describing Agency expectations for application content.

2. **Legislation passed by the European Parliament encourages innovation by providing 10 years of market exclusivity, extendable to 11 years for select new indications of use, for innovator biologics, thereby preventing the introduction of FOBs during that period. Should the U.S. be guided by treatment of drugs and biologics in the EU with respect to exclusivity periods?**

As noted above, the Agency believes that sponsors that develop innovative biotechnology products should be eligible for a significant period of exclusivity protection, independent from any patent protections that might be applicable to the product, to ensure continued innovation. An additional exclusivity period should also be provided if, during the period of exclusivity, the sponsor of the reference product submits, and FDA approves, a BLA supplement for a new indication for which new clinical studies were required (other than bioavailability studies). Such protections should be robust enough to ensure that a follow-on pathway does not negatively impact innovation.

3. **If the U.S. adopts incentives for innovation in biologics that are substantially less than those afforded in Europe, what could the potential effect be on U.S. competitiveness?**
4. **To what extent do you agree or disagree with the EU's current model when it comes to access to needed biologics, patent protection, patient safety considerations (including interchangeability), and the length of time needed for the approval of a new product? What are the advantages and disadvantages of the EU's model? Are there other models that the U.S. can examine? If yes, what are the strengths and weaknesses of their models?**

The Agency has not undertaken an analysis of the effects of the European Union's current model (or other approaches) on access to needed biologics, patent protection, patient safety considerations (including interchangeability), and the length of time needed for the approval of a new product, and therefore is not able to comment.

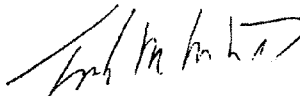
Page 16 – The Honorable Frank Pallone, Jr.

5. **FOBs are now approved in Europe, and FDA has approved a number of follow-on protein products under the FFDCA. Have these shown any problems with respect to safety or efficacy? In what ways are these different from any safety problems seen with brand products?**

FDA has not done a systematic review of all of the follow-on protein products approved under the FD&C Act. In general, FDA does not distinguish postmarket surveillance of brand products from follow-on or generic products. However, FDA's MedWatch Program is an important tool that captures safety information and adverse event reports and helps FDA monitor the safety of all medical products regulated by FDA.

Thank you for contacting us concerning this matter. Please let us know if you have further questions. The same response has been sent to Ranking Member Deal.

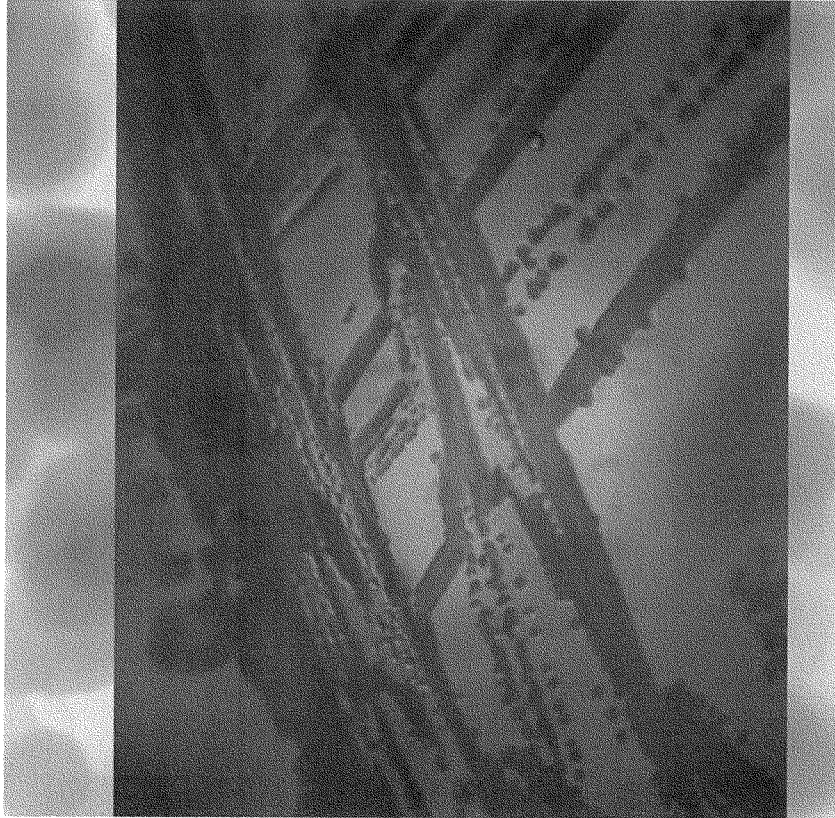
Sincerely,



Frank M. Torti, M.D., M.P.H.
Principal Deputy Commissioner
and Chief Scientist

cc: The Honorable John D. Dingell
Chairman
Committee on Energy and Commerce

The Honorable Joe Barton
Ranking Member
Committee on Energy and Commerce



**PROPER DURATION OF DATA EXCLUSIVITY
FOR GENERIC BIOLOGICS: A CRITIQUE**

by Alex M. Brill

November 2008



Alex Brill is CEO of Matrix Global Advisors, LLC, and a research fellow at the American Enterprise Institute. He previously served as chief economist and policy director to the House Committee on Ways and Means.

I wish to thank Professor Henry Grabowski for sharing data and Scott Ganz for excellent research assistance.

All views expressed are solely those of the author. All rights reserved. Financial support provided by Teva Pharmaceuticals.

ABSTRACT

The future of improved quality and outcomes in healthcare will be dependent on the continued development and availability of biological drugs. Already, \$75 billion in biologics are being sold around the world, and critical therapies from Actimmune to Zevalin are helping patients suffering from illnesses ranging from cancer to arthritis. Biologics, often the most expensive of health care treatment options, have now reached the point that many of them will be coming off patent and market participants are close to developing competitive alternatives, often known as biogenerics, follow-on biologics (FOBs) or biosimilars. In anticipation of these alternatives, a legislative process is under way in Congress to establish an abbreviated pathway for the FDA to grant approval to these biogenerics.

This paper discusses the importance of an appropriate duration for data exclusivity and critiques the recent work by Duke economist Henry Grabowski on this subject (Grabowski 2008). Grabowski estimates the number of years required for an average portfolio of biologic drug investments to recoup all development and fixed production costs and to also reward the investors their expected (double-digit) rate of return. This period of time economists refer to—tongue in cheek, perhaps—as a “break-even” point for the investment.

Grabowski (2008) estimates “break-even” to be between 12.9 and 16.2 years for a portfolio of biologics, and we examine this result and its implication for data exclusivity. First, using an alternative set of assumptions to the Grabowski model that we consider to be more plausible, we find that the “break-even” point drops to slightly less than nine years. Second, the “break-even” point is not the period for sufficient data exclusivity in this industry. Data exclusivity less than the “break-even” point is valid under any assumption in the Grabowski model as long as some economic profits continue to be earned by the innovator drug post-exclusivity; this is reasonable, given expectations for the effect of biogeneric competition on prices. Given our preferred model specifications, we show by example that seven years of data exclusivity would be sufficient in maintaining strong incentives to innovate while fostering a competitive marketplace.

INTRODUCTION

Biological drugs offer some of the most important innovations and benefits for disease treatment, yet are some of the most expensive medical treatments currently offered. While the rapidly rising cost of healthcare will pose a significant fiscal policy challenge in coming years, the therapeutic potential of biologics offers new promise to many of the most debilitating diseases. This dichotomy—critical potential benefit from this class of therapies in comparison to the high cost paid by consumers and, in the case of Medicare and Medicaid, taxpayers—elevates the importance of properly balancing a fundamental public policy tradeoff: policies to foster innovation (new products) against policies to foster competition (lower prices).

At present, the U.S. Congress is considering legislation to create an abbreviated pathway for the FDA to approve biogeneric¹ therapies. Such a pathway already exists for chemical drugs, created in the legislation known as Hatch-Waxman but biologics were generally excluded.² The differences in the manufacturing process for biologic drugs relative to chemical drugs, differences in the R&D expense and product cost, and the potential for both new therapies post-approval and second-generation innovations (“evergreening”) are raising new questions about how to achieve the proper balance between innovation and competition.

One important policy for Congress to establish will be the number of years of data exclusivity awarded to the innovator drug. Data exclusivity rules control the amount of time after an approved drug enters the market that a biogeneric drug, relying on the innovator’s data on drug safety and efficacy, must wait before entering the market. In the case of chemical drugs, that period is generally five years.

A recent article by Duke University economist Henry Grabowski (Grabowski 2008) offers the first attempt to quantify this innovation/competition tradeoff. Grabowski presents an analysis of a portfolio of bio-

logic drugs based on clinical success probabilities, historical R&D costs, average historical sales data and an expected (i.e., “demanded”) rate of return to investors to estimate the average number of years before all the development costs are recouped and a normal profit is earned (where normal profits are equated to the cost of capital for the biopharmaceutical industry). This analysis is referred to in accounting and economics as “break-even analysis” even though it includes profits in the calculation. Grabowski estimates that, given historical costs in the biologic drug industry, the time period in order to “break even” is between 12.9 years and 16.2 years. The variance is due to different assumptions about the cost of capital.

This paper provides an analysis of the Grabowski model and its assumptions. It demonstrates that with more plausible assumptions regarding the cost of capital and the contribution margin, the “break-even” period is considerably shorter. Furthermore, this paper explains that, as a general matter, the “break-even” point should be interpreted as an extreme upper bound for data exclusivity and not as an estimate of optimal duration of data exclusivity. In the case of the biologic drug industry, because innovator drugs can be expected to continue to earn economic profits in a market open to biogeneric competition, optimal data exclusivity will always be less than the “break-even” point. Many readers of Grabowski (2008) falsely interpret that paper’s results.

The remainder of this paper is organized as follows.

Section 1 reviews the growth of biologic drugs in the U.S. and worldwide markets and discusses current developments in the rate of patent expiration for biologic drugs. **Section 2** outlines the theory of optimal patent protection. **Section 3** presents the finance theory used to evaluate business decisions in high-risk investments and explains how to estimate the “break-even” point for a portfolio of investments. **Section 4** presents the finding in Grabowski (2008). **Section 5** explores alternative specifications. **Section 6** discusses the interpretation of the Grabowski model for public policy purposes related to optimal data exclusivity, and **Section 7** concludes.

1 Throughout this paper we use the terms “biogeneric,” “biosimilar” and “follow-on biologics” interchangeably.

2 For a discussion of the FDA approval process for chemical and biological drugs, see Crandall (2008).

1. BIOLOGICS INDUSTRY AND PATENT PROTECTION

Biologics and U.S. healthcare spending. U.S. healthcare spending reached \$2.2 trillion in 2007, 16.3 percent of the total U.S. gross domestic product. Prescription drug spending in 2007 was \$231.3 billion and has been growing about 7 percent per year since 2002 (Center for Medicare and Medicaid Services 2007). Biologic drug spending, roughly 18 percent of total drug spending, has been growing at a rapid 15–20 percent per year (Congressional Budget Office 2008) as new drugs enter the market and additional indications are discovered for existing products. Global sales of biologics were approximately \$75 billion in 2007 (IMS Health 2008). New drug discoveries are increasingly biopharmaceutical products, and it has been estimated that half of all drugs approved in 2010 will be biopharmaceutical.

Biologic drugs offer some of the most promising benefits for a range of life-threatening and crippling diseases, including anemia, hemophilia, cancer, diabetes, HIV, rheumatoid arthritis and thrombosis.

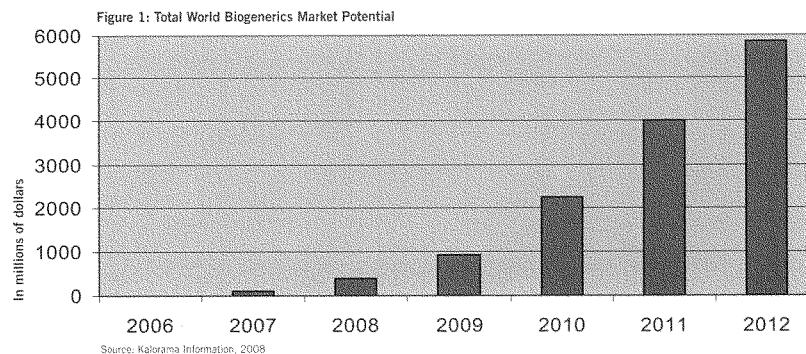
In the last few years, patents for Avonex, Epogen, Neupogen, Novolin and Procrit have expired. A number of biologics will lose their patent protection in the next few years, leading to potential rapid growth in the market for competitor generic drugs.

The world market for biogenics has been projected to reach \$5.8 billion in 2012. Three-fourths of that market will be the result of competition with biologic drugs for which patent protection has already expired. In addition, a number of drug patents, representing over \$10 billion in annual sales currently, will expire over the next four years. Drugs such as Enbrel, Genotropin and Remicade will lose patent protection in the upcoming years and biogeneric research to replicate these products is currently under way (Crandall 2008). Figure 1 below presents the estimated world market potential for biogeneric drugs through 2012 according to research by Kalorama Information (Crandall 2008).

Needed legal framework for follow-on biologics.

While nearly two dozen biologic drugs have lost their patent protection in the last few years and over 70 biologics will lose their patent protection soon, the Food and Drug Administration (FDA) currently does not have an established, abbreviated framework for permitting biogeneric drugs to enter the marketplace. This barrier to competition in the biopharmaceutical marketplace contrasts directly with the structure available for chemical drugs, as established in legislation referred to as the Hatch-Waxman Act³. Hatch-Waxman allows a generic com-

³ The bill's official name is The Drug Price Competition and Patent Restoration Act of 1984 (P.L. 98-417).



petitor to submit to the FDA proof of bioequivalence of the generic to the original drug, known as an abbreviated new drug application (ANDA), instead of being required to undertake a full set of clinical trials.

While the specifics of any legislation should be expected to lead to disagreement between advocates of the patent holder and those advocating for competitive products to come to market, a lack of any established pathway for biogenerics should be a concern for both sides of the debate as the current legal uncertainty creates a real risk that could be suppressing R&D of both innovator drugs and biogenerics. Beyond the importance of establishing *some* pathway for biogenerics, the precise rules and structure of that process will be paramount.

One point of contention among a handful of legislative proposals pending before Congress is the question of duration of data exclusivity. Data exclusivity guarantees that the FDA will not access the data from a drug's trial stages when examining an application of a competitor to sell an identical product. In effect, data exclusivity provisions provide a monopoly period to the drug's developer. Data exclusivity differs from patent protection, which is generally applied for in the preclinical stage and is generally valid for 20 years after the filing date, because data exclusivity is granted when a drug receives final approval from the FDA.

Recent legislative proposals vary along several dimensions, including differing durations of data exclusivity. Representatives Jay Inslee, Gene Green and Tammy Baldwin introduced H.R. 1956 and Senators Gregg, Burr and Coburn introduced S. 1505, which proposes 14 years of data exclusivity. S. 1695, sponsored by Senators Kennedy, Enzi, Clinton and Hatch, would allow for 12 years of data exclusivity. H.R. 5629, sponsored by Representatives Eshoo and Barton, would guarantee 12 years of data exclusivity, with an additional two years for a new indication and six months for pediatric exclusivity. In contrast, recent legislation introduced by Representative Henry Waxman would provide no data exclusivity for new biologics.

2. THEORY OF OPTIMAL PATENT PROTECTION

The purpose of a patent system is to ensure that the inventor of a patented product receives monopoly market conditions and can earn profit margins sufficient to induce the research and development costs associated with bringing the product to market. Nordhaus (1969) is credited with developing the economic framework for calculating optimal patent duration. More recent work, e.g., Tabarrok (2002), has discussed ideas such as varying patent life as a function of the sunk cost required to obtain the patent to yield more efficient outcomes. Lampe and Niblett (2003) discuss the theory of patent protection design broadly and explore game theory approaches in order to capture the dynamic environment when competing firms may be racing to discover and patent a product.

In general, however, the duration of the patent or other patent protections should be chosen to allow for the inventor to charge monopoly rents for a period of time sufficient to induce the initial R&D and other sunk costs.

Two separate intellectual property protections can be granted to new drugs: patent protection and data exclusivity. Their roles in encouraging innovation are different, but each serves an important purpose. Patent protection, granted by the Constitution, generally accrues for 20 years from the date of invention and is granted to an inventor as limited monopoly for new, useful and nonobvious discoveries. Data exclusivity is a definitive monopoly and a government grant, as it allows the innovator's data to be protected without challenge. In the case of chemical drugs, data exclusivity generally lasts for five years from the date a drug is approved by the FDA. Patents can, and frequently are, subject to legal challenge and therefore contain some amount of uncertainty for the patent holder. Data exclusivity is not challengeable in court and therefore is not uncertain.

Because a patent for a drug is granted prior to the marketing of that drug (usually years earlier), the effective patent life will be typically shorter than the statutory 20 years granted for new patents, and the exact effective patent life varies by drug.

One concern over the application and length of data exclusivity would be the determination of eligibility. The length and assignment of data exclusivity in this context could inhibit or encourage what has been described as “evergreening” practices. Evergreening is a process whereby the holder of the patents for a biologic drug, using incremental changes to its original product, is able to shift the market to a newer product so as to limit a generic competitor's market opportunity. If a long period of data exclusivity is applied to each incrementally changed version of the original product, it could result in biogeneric competition being consistently relegated to “older” versions where there is a diminished or exhausted market.

3. INVESTMENT THEORY

The same tools used by investors and corporate project managers to evaluate risky investment portfolios can yield insights for policymakers exploring the impact of data exclusivity rules, but the tools must be applied carefully. The total cost of developing a new biologic drug is driven by two factors: 1) the out-of-pocket R&D costs, including the costs for clinical trials, post-approval clinical costs and fixed costs for establishing the manufacturing facility; and 2) the time value of money driven by the long time periods involved in pharmaceutical R&D. Both factors introduce uncertainty into the total cost of the drug development process. However, the expected revenues from successful development of a biologic drug are, although uncertain, generally quite large. Integrating these expected costs and expected future rewards can be achieved through a cumulative net present value model. A positively valued portfolio is one that will be funded by investors.

By analyzing the expected R&D costs, time for development and approval of a new drug and the expected revenue of a portfolio of investments, one can calculate the number of years of data exclusivity that would yield a “break-even” result. This “break-even” point allows the innovator to earn its required rate of return (e.g., cost of capital) on the risky investment sufficient to induce the R&D.

This paper will focus on “break-even” analysis using a net present value (NPV) approach akin to the model employed by Grabowski (2008).

Net present value modeling of investment decisions.

A simple NPV model allows for an analysis of a project that involves a series of fixed investment costs, k_t , at time $t < 0$ —followed by a series of net future sales, s_t , at time $t > 0$.

By discounting the costs and future returns to the present using a discount rate that reflects the cost of capital for financing the project, the initial cost can be compared to the expected future returns to determine whether a project has a positive net present value. Box 1 provides an example of net present value modeling for investment decisions.

Box 1. An example of a cumulative net present value (NPV) decision model for the development of a new product.

Imagine for example, someone invented a product to automatically tie your shoes. The product took five years and \$500 million to develop but is expected to produce \$850 million in gross margin sales (net revenue) in the five years after it reaches market before becoming obsolete as a result of a new invention. The following table illustrates how to evaluate the expected return from years of development costs for a new product against the subsequent years of net revenues, all discounted (normalized) back to a single time period.

In this example, assuming a 10 percent discount rate, the project has a positive net present value in year 10. However, if one assumes a higher discount rate, say 15 percent, the value of the net revenues in the out years would be reduced and the cumulative net valuation would be negative. This illustrates the sensitivity of NPV calculations in the discount rate. We return to the point in Section 5.

Table 1. Example of NPV calculation

Year	Cost	Net Revenue	Net Present Value	Cumulative Net Present Value
1	-100	0	-100.00	-100.00
2	-100	0	-90.91	-190.91
3	-100	0	-82.64	-273.55
4	-100	0	-75.13	-348.69
5	-100	0	-68.30	-416.99
6	0	100	62.09	-354.89
7	0	150	93.14	-261.76
8	0	200	112.89	-148.86
9	0	200	102.63	-46.23
10	0	200	93.30	47.07

4. GRABOWSKI (2008)

Grabowski (2008) uses a cumulative NPV of discounted cash flows to analyze a portfolio of biopharmaceutical projects. The model is based on estimates of average costs and revenues associated with developing, marketing and selling an average new biologic drug, and the model incorporates average development times for a new product to reach clinical approval. Specifically, Grabowski employs estimates for the model from the following sources:

- Average pre-approval R&D costs from DiMasi and Grabowski (2007).
- Post-approval R&D costs based on Grabowski, Vernon and DiMasi (2002).
- A sales revenue distribution based on Grabowski (2003a, 2003b).
- A contribution margin based on Center for Medicare and Medicaid Services (2003).
- Net revenues and development costs are discounted using two alternative discount rates based on results from DiMasi and Grabowski (2007).

According to these specifications, a portfolio of biologics will have a positive net present value and the investment will break even (including necessary profits incorporated into the model as a cost of capital component) at a point between 12.9 and 16.2 years. Before discussing how this estimate relates to optimal duration for data exclusivity, the paper will next explore alternative specifications to the model.

5. ALTERNATIVE SPECIFICATIONS

Next we turn to a simple sensitivity analysis of Grabowski's results by altering two key variables: the cost of capital (which enters the model as a discount rate) and the contribution margin.

Cost of Capital. As noted in the discussion above, valuations are sensitive to discount rate assumptions. Grabowski's model discounts future cash flows and capitalizes R&D costs using the market-driven cost of capital as the appropriate discount rate. While this approach is valid in theory, we doubt the 11.5 percent and 12.5 percent real discount rates assumed by Grabowski. First, we draw on DiMasi and Grabowski (2007), who report multiple reasons why the real cost of capital for biopharmaceutical companies could fall within the range of 10 percent to 12.5 percent. Their own Capital Asset Pricing Model (CAPM) estimate from a sample of biotech firms (using the methodology explained in Myers and Shyam-Sunder (1995)) indicates that the cost of capital for biotech companies was 10 percent in 2004, the most recent year studied in that paper. Second, Grabowski, et. al. (2002) report that many large pharma firms in 2001–2002 were using *nominal* cost of capital estimates of 12–15 percent, which DiMasi and Grabowski (2007) equate to a 10–12 percent real cost of capital⁴. Third, using real cost of capital estimates compiled by Damodaran (2008) for biotechnology, based on analysis of 103 firms and using current long-term Treasury bill rates, the current real cost of capital for biotech firms is 10.25 percent. Taken together, a real cost of capital in the biopharmaceutical industry is reasonably 10 percent.

Contribution margin. The data for the contribution margin assumption used in Grabowski (2008) is taken from Center on Medicare & Medicaid Services (CMS) report titled "Health Care Industry Market Update: Pharmaceuticals," issued January 10, 2003. That report surveys eight large biotech companies and reports expense and income ratios for 2001. The non-weighted average contribution margin of these firms was 49 percent and Grabows-

⁴ DiMasi and Grabowski (2007) may have made an arithmetic error when they interpret 12–15 percent nominal cost of capital estimates to be equivalent to a 10–12 percent real cost of capital given an inflation assumption of 3 percent. The correct estimate would be 9–12 percent.

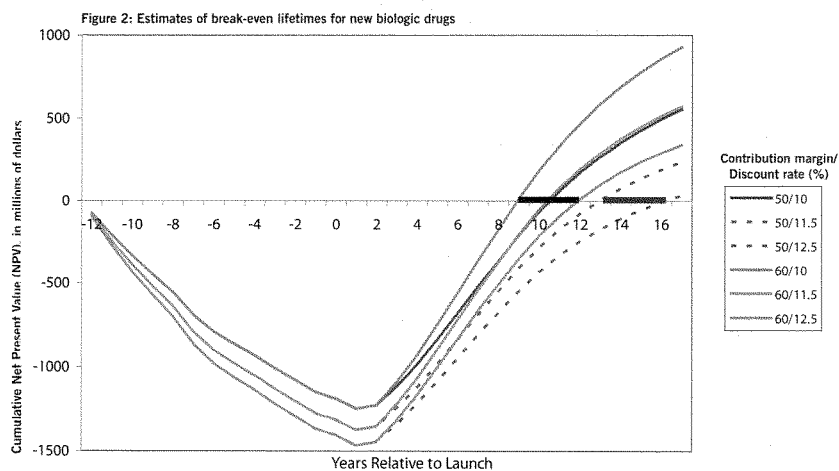
ki uses a similar value of 50 percent in his model. However, contribution margins vary over time and to focus only on 2001, a year in which the U.S. economy was in recession, fails to provide an accurate and current estimate of the contribution margin for the biopharmaceutical industry.

Using financial data reported by Bloomberg, we calculated contribution margins for each of the six largest biotechnology companies⁵ in each of the years 2001 through 2007, in a manner similar to CMS (2003). We then calculated market cap-weighted contribution margin⁶ averages for the industry for each year and average across years. We find that the weighted average contribution margin was 57 percent for all years and 61 percent for the most recent year, 2007. Therefore, we find that 50 percent is too low and consider a contribution margin of 60 percent a more plausible assumption.

Results. Figure 2 below presents a range of results based on additional simulations of the Grabowski model with alternative assumptions. The two dotted lines on the right side of the graph represent the original Grabowski results; specifically a 50 percent contribution margin and an 11.5 percent or 12.5 percent discount rate. The four solid lines represent 50 percent contribution margin and a 10 percent discount rate; and a 60 percent contribution margin with a 10 percent, 11.5 percent or 12.5 percent discount rate. The new results range from just less than nine years to 12 years. Based on assumptions we view as most plausible, a 10 percent discount rate and 60 percent contribution margin, the best estimate of a "break-even" point is at just less than nine years.

⁵ The companies examined are Genentech Inc., Amgen Inc., Glaxo Sciences Inc., Celgene Corp., Genzyme Corp., Biogen Idec Corp. and Biogen Corp. (Biogen is treated by Bloomberg as a separate corporation before its merger with Idec in 2003, so there are seven companies observed in 2001 and 2002.)

⁶ Contribution margins are calculated as the ratio of sales less cost of goods sold less selling, general and administrative expense (SG&A) less R&D to sales.



6. INTERPRETATION AND IMPLICATIONS FOR DATA EXCLUSIVITY

Great care must be taken in interpreting the break-even result for public policy applications related to the optimal duration of data exclusivity rules. Data exclusivity duration should be set so that the portfolio of biologics has a positive expected net present value. Put in the terminology of Grabowski (2008), the portfolio should *eventually* reach a break-even point. Beyond the break-even point, the portfolio is earning profits that exceed the required rate of return expected by investors.

Importantly, the break-even duration will always be greater than the optimal duration of data exclusivity in a market such as biologic drugs, where it can be expected that the innovator drug will continue to earn economic profits following the entrance of biogeneric competition. A number of researchers have estimated the impact of biogenerics on prices and market share (Avalere Health (2007), Grabowski (2007), Express Scripts (2007) and CBO (2008)). In all cases, the prices will not fall to a point where no profits are earned, and in all cases, the innovator drug will maintain a significant market share. Thus, even post-data exclusivity, the innovator will continue to earn rents.

As a result of the fact that economic profits can be earned beyond the break-even point, optimal data exclusivity will be at a time prior to the break-even point. While Grabowski (2008) at no point claims that break-even should be equated with optimal data exclusivity, many readers of his work have made this assertion.⁷

Imposing data exclusivity and limited competition. To explore the impact of data exclusivity on the biopharmaceutical market, we re-estimate a

break-even analysis assuming an impact of prices and market share from competition. We illustrate the effect of seven years of data exclusivity given our preferred assumptions about discount rate and contribution margin.

Additional assumptions about the effects of competition are required for this analysis, and we match our assumption about the effects of competition to the assumptions in CBO (2008)⁸. We assume that market share of biogenerics grows from 10 percent in the first year to 35 percent in the fourth year, and that price (sales-weighted) would decline 20 percent in the first year and 40 percent by the fourth year. The next chart adjusts sales revenues and contribution margins based on these assumptions and recomputes break-even points under the assumption of a 10 percent discount rate and 60 percent contribution margin. It is clear from the graph that investors will still earn their expected rate of return, as the NPV becomes positive in year 10, just one year later than without any competition. Depending on the application of data exclusivity rules, evergreening, the practice described earlier of making small modifications to the original product to extend market control, could further increase profits for the innovator drug but is not considered in this example.

While seven years of data exclusivity does slightly alter the trajectory of the line, the project does still continue to break even (again, this “break-even” point allows for double-digit real rates of return on investment, e.g., the cost of capital). In this case, the “break-even” point increases from nine to 10 years, after which considerable profits are still expected to be realized. Therefore, the incentives to pursue these investments remain.⁹

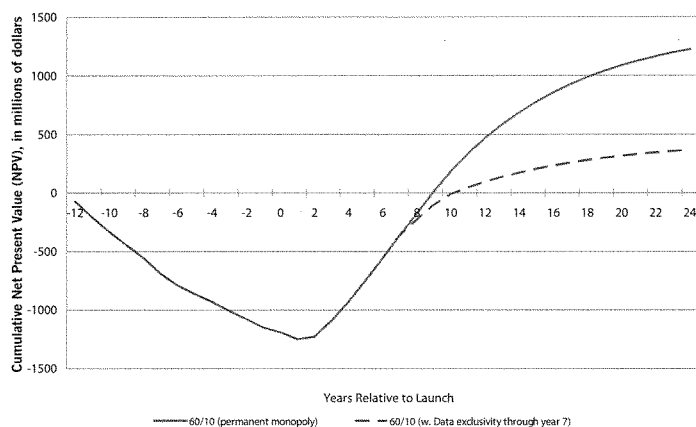
⁷ For example, Wyeth Pharmaceutical, in its letter to the Federal Trade Commission on September 30, 2008, incorrectly stated, “To address the concerns about patent challenges and exclusivity, Grabowski has determined that the appropriate period of data exclusivity for biologics should be 12.9 to 16.2 years.” Amgen, in its letter to the FTC dated September 30, 2008, correctly describes the Grabowski results as relating to break-even analysis but falsely suggests that break-even is equivalent to optimal data exclusivity. Amgen writes, “The break-even point for biologics has been found to occur after it has been on the market somewhere between 12.9 and 16.2 years. Therefore, a 14 year period of data exclusivity is appropriate to recognize this increased cost and provide the proper incentives to invest in products which may fail at any stage in the research and development process.” In testimony to the House Committee on Oversight (Grabowski 2007), Grabowski advocates for a data exclusivity period of “at least ten years in length,” notably different than the position taken by proponents of Grabowski’s work.

⁸ The CBO assumptions regarding the effects of competition on prices for biologics are more conservative than other reports such as Express Scripts (2007).

⁹ For the purpose of sensitivity analysis and to emphasize the result that data exclusivity should be less than the break-even point under any plausible assumptions, we also examined the effect of data exclusivity under alternative assumptions. Assuming a cost of capital of 11.5 percent, a seven-year period of data exclusivity still results in a break-even point.

Figure 3: Examining a 7-year data exclusivity period

Given a 10% discount rate & 60% contribution margin



7. CONCLUSION

Data exclusivity is an important protection awarded to biologic drug innovators and helps ensure adequate incentives for risky and expensive research on disease-curing drugs. However, excessive monopoly protection by the government creates windfalls to innovators, stifles competition and is costly to society. Establishing a pathway for follow-on biologics involves a multitude of policy decisions, and one important choice is the duration of data exclusivity to grant patent holders. Grabowski (2008) establishes a useful framework for estimating the average period of time required for a portfolio of biologics investments to recoup the development cost and reward investors their required rate of return.

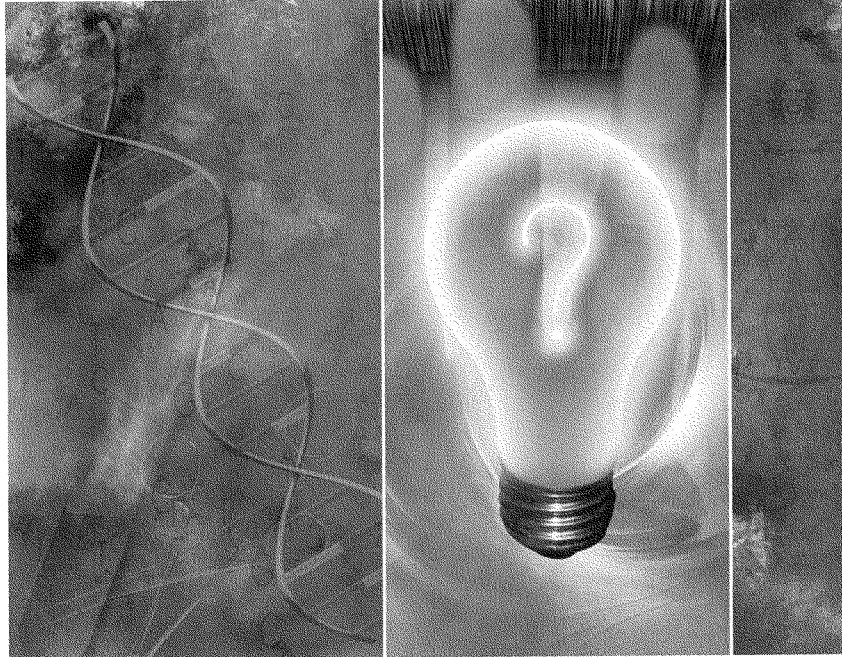
We extend this work in two ways. First, we show that results are susceptible to considerable variation when tested with alternative assumptions. When two key variables, the cost of capital and the contribution margin, are adjusted with more current and plausible estimates, the model indicates that the number of years before break-even is reached is near nine. Second, we explain that this “break-

even” point is beyond the optimal number of years of data exclusivity given the fact that economic profits of the innovator drug are expected to continue following the end of data exclusivity. Assuming that prices and market shares decline according to the assumptions laid out by the Congressional Budget Office (CBO 2008), we find that seven years of data exclusivity would result in a break-even point of 10 years, beyond that point the portfolio continues to earn profits in excess of the required rate of return.

Grabowski (2008) and the variations to that model presented here are stylized approximations of the market for biologics. Important other factors, including other patent protection issues and the aforementioned evergreening issue, not modeled here will affect incentives to innovate and affect the ability of biogeneric competition to improve access to drugs. Nevertheless, a critical factor in any legislation creating a pathway for follow-on biologics will be the duration granted for data exclusivity. Results presented here indicate that seven years is a reasonable duration to balance incentives for innovators with the market benefits of competition.

BIBLIOGRAPHY

- Ahlstrom A., et. al. 2007. Modeling Federal Cost Savings from Follow-On Biologics. Avalere Health, April. http://www.avalerehealth.net/research/docs/Modeling_Budgetary_Impact_of_FOBs.pdf (accessed November 15, 2008).
- Amram, M. and N. Kulatilaka. 2000. Strategy and shareholder value creation: the Real Options frontier. *Journal of Applied Corporate Finance*. Bank of America, Summer, 8–21.
- Centers for Medicare and Medicaid Services. 2003. Health Care Industry Market Update: Pharmaceuticals. January 10. <http://www.cms.hhs.gov/CapMarketUpdates/Downloads/hcimul11003.pdf> (accessed November 14, 2008).
- Centers for Medicare and Medicaid Services. 2007. National Health Expenditure Projections 2007–2017. <http://www.cms.hhs.gov/NationalHealthExpendData/Downloads/proj2007.pdf> (accessed November 14, 2008).
- Congressional Budget Office (CBO). 2008. S. 1695: Biologics Price Competition and Innovation Act of 2007. Congressional Budget Office Cost Estimate, June 25. <http://www.cbo.gov/ftpdocs/94xx/doc9496/s1695.pdf> (accessed November 13, 2008).
- Crandall, M. 2008. Biogenics: The World Market for Biosimilars. Kalorama Information, April.
- Damodaran, A. 2008. Discount Rate Estimation: Costs of Capital by Industry Sector, The data page. Damodaran Online, January. <http://pages.stern.nyu.edu/~adamodar/> (accessed November 15, 2008).
- DiMasi, J.A. and H.G. Grabowski. 2007. The cost of biopharmaceutical R&D: is biotech different? *Managerial and Decision Economics* 28: 469–479.
- Fama, E.F. and K.R. French. 1993. Common risk factors in the returns on stocks and bonds. *Journal of Financial Economics* 33: 3–56. <http://home.business.utah.edu/finml/fin787/papers/FF1993.pdf> (accessed November 7, 2008).
- Golec, J.H. and J.A. Vernon. 2007. Financial risk in the biotechnology industry. National Bureau of Economic Research Working Paper 13604, November. <http://www.nber.org/papers/w13604> (accessed November 7, 2008).
- Grabowski, H.G. 2003a. Patents and new product development in the pharmaceutical and biotechnology industries. *Georgetown Public Policy Review* 8: 7–24.
- Grabowski, H.G. 2003b. Patents and New Product Development in the Pharmaceuticals and Biotechnology Industries. In *Science and Cents: the Economics of Biotechnology*, eds. J.V. Duca and M.K. Yucel, Federal Reserve Bank of Dallas, 87–104. <http://www.dallasfed.org/research/pubs/science/science.pdf> (accessed November 14, 2008).
- Grabowski, H.G. 2007. Testimony to House Oversight and Government Reform Committee. March 26.
- Grabowski, H. G. 2008. Follow-on biologics: data exclusivity and the balance between innovation and competition. *Nature Reviews Drug Discovery*. Advance Online Publication, 12 May. <http://fds.duke.edu/db?attachment-25-1301-view-503> (accessed November 14, 2008).
- Grabowski, H.G., J. Vernon and J. DiMasi. 2002. Returns on research and development for 1990s new drug introductions. *Pharmacoeconomics* 20 (Supplement 3): 11–29.
- Liang, Brian A. Don't compromise the safety of biotech drugs. *Los Angeles Times*, April 24, 2008. <http://www.latimes.com/news/opinion/la-oe-liang28apr28.0.6509922.story> (accessed November 14, 2008).
- Lampe, R. and Niblett, A. 2003. The Economics of Patent Design: A Select Survey. IPRIA Working Paper. No. 06/03.
- Miller, S. and J. Houts. 2007. Potential Savings of Biogenics in the United States. *Express Scripts*, February.
- Myers, S.C. and L. Shyan-Sunder. 1995. Measuring pharmaceutical industry risk and the cost of capital. In *Competitive Strategies in the Pharmaceutical Industry*, ed. R.B. Helms. Washington, D.C.: American Enterprise Institute.
- Pandey, M. 2003. Investment decisions in pharmaceutical R&D projects. *Drug Discovery Today* 8 (21): 968–971.
- Tabarrok, A. 2002. Patent Theory versus Patent Law. *Contributions to Economic Analysis & Policy* 1(1), article 9.



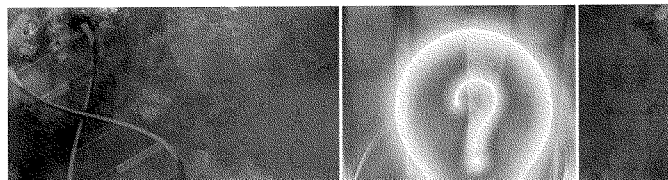
**Stimulating Innovation in the Biologics Industry:
A Balanced Approach to Marketing Exclusivity**

by **Laurence J. Kotlikoff**

Professor of Economics
Boston University

September 2008





Stimulating Innovation in the Biologics Industry: A Balanced Approach to Marketing Exclusivity¹

Executive Summary

New and improved medications are critical to Americans' health and welfare. Today, the most significant, but also most expensive, advances in medications come in *biologics*. Biologics are protein-based, rather than chemical-based, medicines. The new drugs can be of tremendous help in alleviating, if not curing, a wide range of heartbreaking diseases. At the same time, their prices are remarkably high, leaving millions of uninsured and underinsured Americans unable to access their use.

As policymakers in Congress debate legislation to create an approval pathway for affordable biologic medicines, a strong case has been made regarding the potential savings and increased access that will result. These savings could run in the tens of billions of dollars annually and have a significant impact on access for patients. They would also dramatically lower costs to health care purchasers, be they payors from private industry or the government — the single largest purchaser of prescription medications.

The key issue in providing affordable access to biologic wonder drugs is doing so without limiting their development. This paper focuses on how best to encourage continued innovation in this sector by providing the appropriate degree of monopoly protection. Four bills pending in Congress propose to do for biologic medications what the 1984 landmark Hatch-Waxman bill did for chemical medications, namely, promote a competitive marketplace that would dramatically lower prices while also ensuring strong incentives to innovate. Yet three of the four bills contain *exclusivity* provisions that run the danger of overextending monopoly protection. Doing so would, paradoxically, undermine innovation and the bills' own objectives.

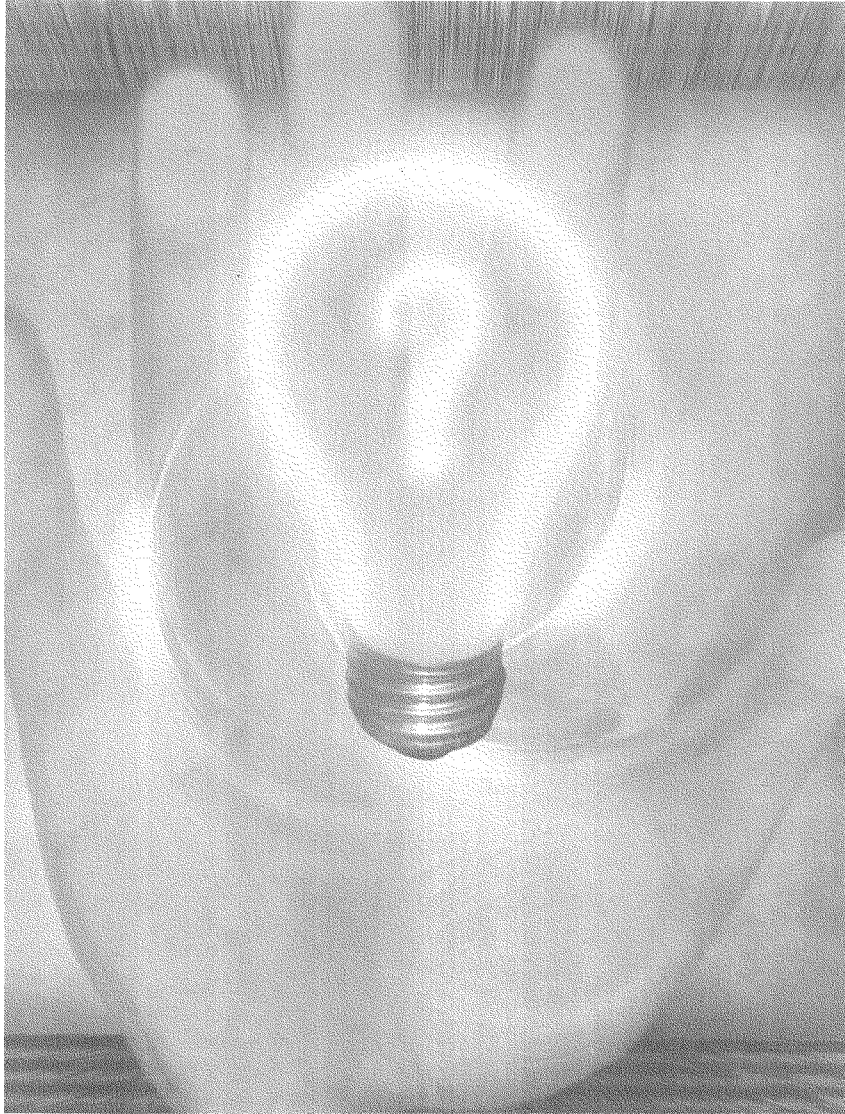
Bestowing lengthy monopolies by statute on brand biologic companies not only greatly delays entry by competitors with low-cost alternatives, but also excludes other innovators from building — in a timely manner — on the stock of prior knowledge — much of which was accumulated at public expense.

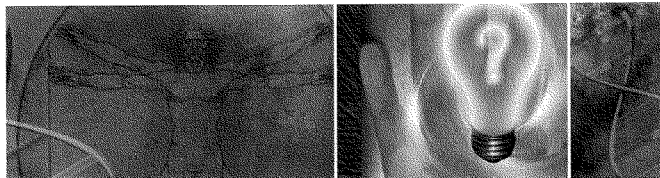
New medications that alleviate or cure terrible disease are such remarkable gifts that we all want to do everything possible to continue their discovery. But the new drugs of today are not those of tomorrow. The reason is clear. Today's inventors have strong incentives to protect their discoveries, not to make new ones whose arrival on the market would undermine their existing profits.

Numerous papers in the economics literature on invention and monopoly protection stress that competition, not protection, is the true source of innovation and that overextending monopoly protection can be counterproductive. It may do little or nothing to incentivize new discovery, and may simply delay when the next discovery comes on board. Thus, rights to exclusive marketing periods can lead to less, not more, innovation over time. This is particularly true given the potential to use exclusivity periods to "evergreen" one's products — to secure additional long periods of monopoly based on minor product modifications.

Hatch-Waxman has proved remarkably successful in balancing incentives to innovate with the need for access to new medicines. Given this success and the absence of any material differences between the biologics and chemical medical industries arguing for longer monopoly protection, Congress should consider the Hatch-Waxman model for exclusivity rather than proposals that would distort the market and undercut innovation.

¹ I was asked by Teva Pharmaceuticals USA, which provided the funding for this study, to assess the impact of varying lengths of market exclusivity on innovation in the context of the biotechnology sector. The views expressed here are those of mine and not necessarily those of Teva Pharmaceuticals USA.





Introduction

New and improved medications are a vital and growing part of America's \$2 trillion healthcare system.² Today, one of every 10 healthcare dollars is spent on prescription drugs, compared to one of every 20 in 1980.³ The nature of medicines is also changing. The most significant, but also most expensive, advances are coming in *biologics*.

Biologics are protein-based, rather than chemical-based, medicines.⁴ When Americans take pills, capsules, and liquid medications, they are taking chemical compounds. But for many serious illnesses, they increasingly rely on injections and infusions of biologics.

The new drugs can be of tremendous help in relieving pain and suffering. In some cases they represent miracle cures. But their prices are staggering. Biologics cost, on average, 22 times more per daily dose than chemical medications;⁵ the most expensive biologics cost over \$100,000 a year. The public's annual bill for biologics has been growing at a 15 percent rate, with this year's total exceeding \$40 billion.⁶

For those lucky enough to gain access to these new super-expensive but often highly effective medications, there is real hope. Biologics are now fighting arthritis, asthma, Alzheimer's, heart disease, Crohn's disease, several cancers, psoriasis, multiple sclerosis, Lou Gehrig's disease, and AIDS. And if innovation continues, new biologics will be developed to battle the full range of cancers as well as a host of other diseases.

The *if* here is a big one. Innovation in biologics is now threatened, ironically, by specific exclusivity provisions in what is otherwise

long-overdue legislation to provide Americans with accessible alternatives to extraordinarily high-priced brand biologic medicines.⁷

The exclusivity provisions come in two forms — *data exclusivity* and *approval exclusivity* (often referred to as *market exclusivity*). Both extend the duration of monopoly protection afforded brand drug products; i.e., both convey *marketing exclusivity*. And both depart very sharply from longstanding U.S. policies in balancing intellectual property protection and the U.S. economy's lifeblood — competition.

The proposed legislation comprises four bills before Congress. Each bill authorizes the Food and Drug Administration (FDA) to do for biologic medicines what it's been doing under the Hatch-Waxman Act of 1984 for chemical-based medicines, namely expedite approval of generic alternatives to drive down prescription costs.⁸

Biologics cost, on average, 22 times more per daily dose than chemical medications;⁵ the most expensive biologics cost over \$100,000 a year.

The bills are *Access to Life Saving Medicine Act* (S623/HR1038), introduced by Congressman Henry Waxman and Senator Charles Schumer; *The Biologics Price Competition and Innovation Act of 2007* (S1695), introduced by Senator Edward Kennedy; *The Pathway for Biosimilars Act* (HR 5629), introduced by Congresswoman Anna Eshoo and Congressman Joseph Barton; and *The Patient Protection and Innovative Biologic Medicines Act of 2007* (HR1956), introduced by Congressman Jay Inslee.

The stated goal of each bill is to foster a robust generic biologics industry. But provisions in the Kennedy bill conveying four years

² Centers for Medicare and Medicaid website. http://www.cms.hhs.gov/NationalHealthExpendData/02_NationalHealthAccountsHistorical.asp, accessed on 27 June 2008.

³ *Ibid.*

⁴ Eprex, which treats anemia, is an example. It's produced by extracting proteins from animal cells and replicating them in vitro. Neuturin, which targets heartburn and acid reflux, is produced by combining chemical compounds with no reliance on animal tissue.

⁵ *Ibid.*, p. 17.

⁶ <http://www.hhs.gov/fpo/docs/0406/roa3496/s1695.pdf> This expenditure is being made primarily via third-party insurers or the government.

⁷ The European Union created a new regulatory pathway for follow-on biologics in 2005. By 2010, when a number of brand biologics go off patent in the EU, we should see significant biologic generic entry.

⁸ The European Union passed such legislation in 2005. As a result, Europeans can now access low-cost generic versions of a number of leading biologics, including Eprex.

of data exclusivity followed by eight years of approval exclusivity, provisions in the Eshoo-Barton bill conveying 12 years of data exclusivity followed by two years of approval exclusivity, and provisions in the Inslee bill also conveying 12 years of data exclusivity followed by two years of approval exclusivity could delay by years the advent of low-cost generic alternatives.

Ongoing evergreening of biologics can extend their monopoly protection far into the future. Such “innovation” blocks true discoveries that would materially improve the public’s health, and undermine existing product sales.

Most importantly, the exclusivity provisions could stifle the discovery of new biologic treatments for the terrible afflictions just mentioned. This is particularly true in light of the industry’s ability to evergreen its drugs – to spend the time afforded by initial monopoly protection to make minor modifications to the biologic’s formulation and, thereby, garner extra periods of statutory exclusivity. Ongoing evergreening of biologics can extend their monopoly protection far into the future. Such “innovation” blocks true discoveries that would materially improve the public’s health, and undermine existing product sales.

Given the medical and economic stakes involved, it’s important for Congress to consider carefully the potential for exclusivity provisions to significantly retard innovation in biologics by undermining the ability of competitors to offer low-cost, competing products in a meaningful time frame.

This paper pursues this objective. It begins by briefly questioning two presumptions when it comes to monopoly protection policy and the drug industry. The first is that longer periods of monopoly protection necessarily promote innovation. The second is that extending the duration of monopoly protection, while it may have winners and losers, causes no overall economic loss, i.e., no economic inefficiency.

These questions provide the context for the next task – assessing the exclusivity provisions specially designed for the brand biologic companies and explaining how exclusivity provisions in three of four biogenerics bills would dramatically extend monopoly protection afforded to brand biologics.

But my main focus will be to amplify the point raised immediately below, namely, that extended periods of exclusivity pose a

threat to sustaining a rapid rate of innovation. This analysis forms the basis for my recommendation that when it comes to promoting biologic competition Congress should stick with what works, namely Hatch-Waxman, with its very limited exclusivity.

Economic theory speaks clearly here. So does the evidence. There are, quite simply, no compelling differences between the chemical-based and protein-based medication industries to justify deviating from a policy that has succeeded for over a quarter of a century in both dramatically reducing drug prices and stimulating innovation.

Indeed, to the extent there are differences, they generally favor less exclusivity. A key example here is the likelihood that obtaining FDA approval of generic biologics will take considerably longer than obtaining FDA approval of a chemical entity.⁹ If this proves true, it will automatically provide brand companies with an extended period of effective exclusivity even absent any legislated exclusivity.

Can Extended Periods of Exclusivity Threaten Innovation?

Raising this question may sound surprising given that some period of exclusive marketing rights is required to incentivize discovery. But starting a train is not the same as keeping it moving, let alone getting it to run at the proper speed. When it comes to innovation, each “discovery” builds on prior knowledge, with progress measured by the next innovation, not the last, and by how fast the next innovation gets to market.¹⁰

Policies that lengthen the time between innovations may do little to stimulate more innovation; instead, they may simply reduce the pace of innovation (the number of discoveries per unit of time) on which the economy’s growth so critically depends.

The key problem with providing excessive monopoly protection is that once an invention has been made, the inventor faces different incentives. The main goal becomes marketing and protecting one’s intellectual property, not developing a dramatically different and better version of the product. Doing so would diminish, if not vitiate, the value of the initial invention, which may have been undertaken at considerable cost. Hence, at least within a given product line, yesterday’s inventors are much less likely to be either today’s innovators or tomorrow’s.

This point comes across clearly in the economics literature starting with the seminal 1959 paper on intellectual property by Nobel

⁹ Shapiro, Robert, op. cit., p.4.

¹⁰ Isaac Newton paid deference to this process in his famous statement: “If I have seen further it is by standing on ye shoulders of Giants.”

laureate Kenneth Arrow.¹¹ In the years since Arrow showed that "the incentive to invent is less under monopolistic than under competitive conditions," numerous economists have developed alternative models of the innovation process, but they invariably reach the same conclusion — *monopolists don't innovate*. The reason is simple: bringing new products to the market undercuts a monopolist's revenues on his existing products.

Distorting the Economy via Excessive Monopoly Protection

Prolonged monopoly protection raises additional concerns. It distorts consumer choice by maintaining artificially high prices of those final goods and services that are being protected. The same point applies to all the monopoly-protected inputs purchased by businesses. If their prices remain too high for too long, too few of the inputs will be used in production. The result will be a production distortion.

Distortion arising from excessively long monopoly protection is called *rent seeking*. In the context of inventing, the rent seekers are the inventors and the rent they seek is the monopoly profits from their discoveries. For those winning the race to discovery, the rewards are great. But all those losing the race have expended resources, potentially very large amounts of resources, for naught. To be clear, some losers and losses are inevitable. The issue is how many would-be inventors, with what size losses, monopoly-protection policy will create.

Another distortion, which arises in the context of biologics, involves access. Because biologics are so expensive and because America has so many uninsured and underinsured people with limited access to these medications, those with access to these medicines may not have the most need for them. There is clearly an equity issue here. But there is also a separate issue of efficiency. Markets in which some people face one set of prices for goods and services and other people face another set are inefficient for a simple reason — there are beneficial economic trades between the two sets of people that are not occurring.

These economic and other distortions discussed in this paper are important. Economists reference them as *excess burdens*, *dead-weight losses*, or *economic inefficiencies*. But no matter what they are called, these distortions entail real economic costs to society. Concern about these efficiency costs explains why we restrict monopolies, why we have patent limits, why we have free domestic trade, and why we form free trade agreements.

Data Exclusivity, Approval Exclusivity, and Marketing Exclusivity

As introduced in part of Hatch-Waxman, *data exclusivity* refers to a period of time during which a potential generic supplier of a brand drug is prohibited from filing for an ANDA (Abbreviated New Drug Application).¹² This prohibition is a type of gag order. It is effectively conveyed by preventing potential generic suppliers from using publicly available clinical trial and related data to substantiate the safety of their medically equivalent/similar medicines.

Approval exclusivity, sometimes referred to as *market exclusivity*, is a period of time during which a generic drug supplier can file for FDA approval, but cannot receive approval. In other words, FDA approval is exclusively limited to brand companies during this period even if all prerequisites for FDA approval of generic alternatives have been established.

Since data exclusivity prevents even seeking FDA approval and approval exclusivity prevents receiving FDA approval, even if one has sought it by substantiating medical equivalence/similarity, both data exclusivity and approval exclusivity constitute *marketing exclusivity* — periods during which brand companies are exclusively permitted to market the medication in question.

Prolonged monopoly protection raises additional concerns. It distorts consumer choice by maintaining artificially high prices of those final goods and services that have been patented.

Being able to file for FDA approval, even during periods when the FDA is precluded from granting approval, is important. Generic drug suppliers may not be able to contest the patents of a brand provider *unless* the generic supplier has filed with the FDA. Consequently, *data exclusivity* represents absolute monopoly protection for brand suppliers — monopolies that are granted even if a brand's patents are found to be invalid following judicial review.

Using data exclusivity periods to prevent the courts from adjudicating patent challenges goes well beyond standard patent protection policy provided under GATT. Indeed, providing data exclusivity is tantamount to the government simply doing away with patents altogether and conveying exclusive product marketing rights to favored companies by fiat. Such a policy is at considerable odds with the principles of free markets.

11. Arrow, Kenneth J., "Economic Welfare and the Allocation of Resources for Invention," Rand Corporation working paper P-1855-40, December 15, 1959.

12. To be precise, the FDA is prohibited during the period from using the brand company's safety and effectiveness findings (data) as a basis for approving medically equivalent generic alternatives.

As indicated, approval exclusivity comes into play after data exclusivity expires. Although approval exclusivity permits competing drug companies to file their product applications with the FDA and, in the process, potentially contest the validity of patents of drugs already on the market, it tells competitors that no matter whether they win their patent fights or not, they will not get to market until this extra protection period has run its course.

Given Hatch-Waxman's significant patent restoration provision, its exclusivity will rarely extend the total length of monopoly protection.¹³

The clock on the total period of data plus approval exclusivity starts with FDA approval of the brand drug. The reason is that the exclusion is determined with respect to the filing and approval of ANDAs. But an ANDA presupposes an NDA (a New Drug Application); the government's exclusivity clock doesn't start until the government approves the new brand drug and allows it to go on the market.

The upshot here is that if the total period of exclusivity exceeds the amount of patent protection left at the time of FDA NDA approval, monopoly protection will be expanded by the number of years that exclusivity exceeds remaining patent life.

Take, for example, a new biologic that receives FDA approval 12 years after initial patent filing. Under GATT, the biologic should receive eight more years of patent protection (20 years total less the 12 years already elapsed). But were the Eshoo-Barton or Inslee bills passed, the biologic would qualify for 14 years of exclusivity beyond the date of FDA approval. Since 14 exceeds eight, the biologic would receive 14 years of protection post-FDA approval rather than eight. And since 14 plus 12 equals 26, the biologic ends up with 26 years, rather than 20 years, of monopoly protection. This represents a 30 percent increase in monopoly protection relative to the GATT norm — the standard protection being provided to inventions of all other goods and services apart from drugs!

Exclusivity, Patent Restoration, and Marketing Stays under Hatch-Waxman

The Hatch-Waxman Act does provide for data and approval exclusivity for chemical entities, but on a much more limited basis than that proposed in the Kennedy, Eshoo-Barton, and Inslee generic biologics bills. Instead of the combined data plus approval exclusivity periods of 12 years (four data plus eight

approval) years proposed in the Kennedy bill and 14 years (12 data and two approval) proposed in both the Eshoo-Barton and Inslee biologics bills, Hatch-Waxman offers five years of exclusivity generally, with four years of data exclusivity followed by one year of approval exclusivity if an applicant files a patent challenge in the fourth year. The Waxman biologics bill does not address data or approval exclusivity whatsoever.

The Hatch-Waxman Act also provides for *patent restoration*; the Act restores to a new chemical entity's patent life half of the time spent in clinical testing and all of the time spent securing FDA approval, up to a maximum of five years. The amount of patent restoration is also subject to a ceiling: total patent life beyond FDA approval cannot exceed 14 years. Thus, a new chemical drug that receives FDA approval after 12 years from initial patent application, having spent four years in clinical trials and two years undergoing FDA review, has three years of patent restoration time tacked onto the standard 20-year patent term provided under GATT. This provides the drug with 24 years of patent life, of which 12 is post-FDA approval.

In contrast, if FDA approval had occurred eight years from patent application, six of which again had been spent in trials and FDA review, the patent would be extended by only two years — to 22 years total — because any longer extension would mean more than 14 years of patent life beyond the date of FDA approval.¹³

Given Hatch-Waxman's significant patent restoration provision, its exclusivity will rarely extend the total length of monopoly protection.¹⁴ But it does delay by at least four years the ability of competitors to contest the patents of brand companies. Another feature of Hatch-Waxman that delays competitors in overturning invalid patents and quickly getting to market is the ability of brand companies to have the courts automatically stay FDA approval of an ANDA for two and a half years if the brand company sues the competitor for patent infringement.

Hatch-Waxman's Applicability to Biogenics

It's important to realize that one portion of Hatch-Waxman, namely patent-term restoration, applies to biologic medications as well as chemical medications, even though there is currently no pathway for generic biologics to receive FDA approval and reach market. And since none of the biologics bills abrogate Hatch-Waxman's provisions, brand biologics, under all of the bills, will still retain patent restoration. Hence, under all but the Waxman biologics bills, brand biologics will enjoy four legislated types of monopoly protection — GATT, data exclusivity, approval exclusivity,

¹³ As these two illustrations indicate, drugs brought to market early are being penalized by these provisions relative to those brought to market late. Providing incentives to delay the introduction of new medications seems a significant deficiency in the Hatch-Waxman Act.

¹⁴ Grabowski, Henry G., and John M. Vernon, "Effective Patent Life in Pharmaceuticals," *International Journal of Technology Management*, Vol. 13, 2000, p. 116, states that "The effects of Waxman Hatch and GATT on EPL (effective patent life) have been modest to date."

Table 1: Years of Monopoly Protection from Date of Patent Application

Years between Patent Application and FDA Approval of Brand Drug	GATT – Non-Drugs	Hatch-Waxman Chemical Drugs	Waxman Biologics Bill	Kennedy Biologics Bill	Eshoo-Barton Bill	Inslee Biologics Bill
6	20	20	20	20	23	23
8	20	22	22	22	25	25
12	20	23	23	24	29	29
16	20	23	23	28	33	33
20	20	25	25	32	37	37

Table assumes no evergreening, incorporates exclusivities, and assumes five years for testing and approval of biosimilars (see Shapiro, 2008) commencing at ANDA filing and a three-year patent restoration period.

and patent restoration. Each of these protections can impact the total length of monopoly protection depending on the particular circumstances involved. Under the Waxman bill, brand biologics would enjoy GATT and patent restoration protections.

The Proposed Expansion of Monopoly Protection for Biologics

Table 1 examines the duration of monopoly protection that each of the biogenerics bills would extend to brand biologics companies under different assumptions about the amount of time brand companies spend between submitting a patent and achieving FDA approval of their product.

The table takes into account GATT's 20-year patent duration rule, exclusivity provisions, patent restoration, and the time required for biologic generic companies to receive FDA approval of their medically similar alternatives. I assume that, starting from the end of the period of data exclusivity, it would take biologic generic companies five years to develop a generic biologic, file for FDA approval, and receive FDA approval.¹⁵

For purposes of comparison, the table shows the duration of monopoly protection under pure GATT treatment (the treatment of non-drug products) and under Hatch-Waxman Act treatment (the treatment for new chemical entities). In calculating the length

of protection under Hatch-Waxman, I assume a three-year patent restoration extension – the average such extension calculated by the Congressional Budget Office.¹⁶ Finally, I ignore the potential of brand companies to receive FDA-approval stays and to evergreen their products.¹⁷

In considering table 1's findings, it's important to bear in mind that innovations build on one another. Hence, permanently lengthening monopoly protection from 20 to, say, 25 years represents a 25 percent permanent delay in the advent of the next (the second) innovation. In this case, the second innovation arrives five years late, the third 10 years late, the fourth 15 years late, etc. Over the course of a century, the country experiences not five innovations, but four. And successive generations end up being harmed to an ever-increasing degree.

Compare, to begin, the standard 20-year GATT monopoly protection period with the 29-year period provided under the Eshoo-Barton and Inslee biologics bills, assuming the brand biologic company expends 12 years achieving FDA approval. The difference between 29 years and 20 years is 45 percent. This is a very substantial deviation from GATT and has the potential to substantially reduce the pace of innovation.

Under the Kennedy bill, the duration of monopoly protection for this case is five years shorter, i.e., 24 years. The difference reflects the two-year shorter length of total exclusivity under the

¹⁵ See Shapiro (2008), op. cit.

¹⁶ Congressional Budget Office, "How Increased Competition from Generic Drugs Has Affected Prices and Returns in the Pharmaceutical Industry," July 1998, table B, p. 40.

¹⁷ These stays appear to have the potential to add another half year of monopoly protection under the Eshoo-Barton and Inslee bills for all cases considered in table 1.

Table 2: Years of Marketing Exclusivity from Date of Patent Application

Years between Patent Application and FDA Approval of Brand Drug	GATT – Non-Drugs	Hatch-Waxman Chemical Drugs	Waxman Biologics Bill	Kennedy Biologics Bill	Eshoo-Barton Bill	Inslee Biologics Bill
6	14	14	14	14	17	17
8	12	14	14	14	17	17
12	8	11	11	12	17	17
16	4	7	7	12	17	17
20	0	5	5	12	17	17

Table assumes no evergreening, incorporates exclusivities, assumes five years for testing and approval of biosimilars commencing at ANDA filing, and assumes a three-year patent restoration period.

Kennedy bill compared to the Eshoo-Barton and Inslee bills and the fact that the Kennedy bill allows filing for ANDA after four years as opposed to after 12 years in the Eshoo-Barton and Inslee bills. Under the Kennedy bill, generic biologic firms would, I assume, spend the eight years after filing, but before being able to receive final FDA approval, in doing the testing under FDA supervision needed to obtain final approval once the eight years of approval exclusivity had run its course.¹⁸

Compared with the Eshoo-Barton and Inslee bills, the Kennedy bill entails shorter monopoly protection. But monopoly protection under the Kennedy bill is still much longer than under Hatch-Waxman in the case the brand company takes more than 12 years to get to market. Remarkably, the Kennedy, Eshoo-Barton, and Inslee bills reward delay in getting to market with longer monopoly protection, with each year of delay beyond 12 leading to roughly one more year of protection. One wonders why legislators would want to encourage delay in the pace at which innovative drugs are brought to market and lower the speed at which today's innovations are incorporated in tomorrow's discoveries.

Table 2 puts this point in higher relief. It shows the duration of marketing exclusivity available to the biologic brand company for different periods of time the brand takes to get to market. Note that Hatch-Waxman and the Waxman biologics bill penalize delays

in reaching the market by reducing monopoly protection by roughly one year for each year of delay.

Can table 2's huge differences in marketing exclusivity periods for a) chemical medications subject to Hatch-Waxman and b) biological medications under either the Kennedy, Eshoo-Barton, or Inslee bills be justified by much longer startup times for new biological entities compared with new chemical entities? The answer is no. As Henry Grabowski has shown, the average development time for new biological entities is only 7.4 months longer than that for new chemical entities.¹⁹ In comparison, relative to Hatch-Waxman, the Eshoo-Barton and Inslee bills call for between 12 months and 120 months of extra monopoly protection depending on when the biologic is brought to market.

What about costs and risk? Do either of these factors justify longer monopoly protection for biologics than chemical entities?

The answer is no. Consider first the issue of cost. There is no question that bringing a new biologic medication to market is exceptionally expensive — an estimated \$1.24 billion.²⁰ But cost per se is not economically relevant. What matters is cost relative to reward. Invention X may cost \$1 million to bring to market and invention Y \$1 billion, but the projected revenues for Y may exceed those for X by far more than a factor of 1,000. In this case, less

¹⁸ Note that patent restoration does not extend the length of monopoly protection in this case, since it adds, by assumption, three years to the GATT's 20, which equals 23, which is less than 24.

¹⁹ Grabowski, Henry. "Follow-On Biologics: Data Exclusivity and the Balance Between Innovation and Competition." *Nature Reviews Drug Discovery*, Volume 7, June 2008.

²⁰ See DiMasi, Joseph A., Ronald W. Hansen, and Henry G. Grabowski. "The Price of Innovation: New Estimates of Drug Development Costs." *The Journal of Health Economics*, Volume 22, Issue 2, March 2003, pp. 151-185 and Grabowski, Henry. "Follow-On Biologics: Data Exclusivity and the Balance Between Innovation and Competition." *Nature Reviews Drug Discovery*, Volume 7, June 2008. \$802 million is, by the way, the estimated cost of bringing a new chemical medication to market.

monopoly protection is needed to promote invention of Y than of X.

Compared with pharmaceuticals, biologics are more costly to produce. But their reward is also considerably higher. Indeed, compared to chemical medications, biologic medications appear to have a lower ratio of invention cost to invention reward.²¹ Moreover, there is no presumption in the economics literature on optimal monopoly protection that products entailing higher cost relative to reward should be provided longer periods of protection.

Next, consider risk. Only one in five of all drugs tested clinically makes it to market,²² with the success rate possibly lower in biologics. But modern finance teaches us that collections of individual investments, each of which is highly risky, can, thanks to the law of averages (law of large numbers), be quite safe. If only one in 20 experimental drugs makes it to market, but you experiment with 1,000 such drugs, you can be pretty sure that close to 50 will be successful. Stated differently, the risk that most advocates of longer monopoly protection cite as supportive of such a policy is *diversifiable risk* – risk that is diversified away in the financial marketplace and that doesn't raise the cost of capital confronting biotech companies.²³

When it comes to *non-diversifiable risk*, the biotech industry is riskier than most, but not by much. Consequently, the cost of equity capital in biotech is only 18 percent higher than the average across all other industries. Moreover, a quarter of U.S. industries are riskier than biotech, but none of these garner longer monopoly protection. The appendix lists the 25 industries with higher costs of equity capital than biotech. The semiconductor industry is the most risky, with a cost of capital 89 percent above the average. The pharmaceuticals industry, interestingly enough, is much riskier than biotech. Its cost of capital is 35 percent above average.²⁴

Evergreening

Evergreening will multiply the economic costs of expanding monopoly protection via exclusivity arrangements. Brand companies can, and routinely do, make relatively minor changes to their existing products in order to restart their monopoly-protection clocks. These changes include changing the medication strength of pills (e.g., changing the pills from .10 mg to .15 mg), changing the form of medication (e.g., switching from pill to capsule),

modifying the method of delivery (e.g., from injection to inhalation), expanding indications (applying the medicine to additional conditions), pegylation (which has the effect of reducing doses per time period via time-release mechanisms), and glycosylation (adding sugar molecules to the medication).

To understand the risk evergreening poses to true innovation and competition in the industry, suppose either the Eshoo-Barton or Inslee bill is passed and a brand biologic company called BioBrand, Inc., spends 12 years getting its biologic drug produced, tested, and FDA-approved. According to table 1, 17 years later (29 years after the patent is initially filed) generic competitors will finally be able to bring a competing medication to market.

Or will they? Given evergreening, BioBrand can readily come up with a small change along one of the aforementioned product characteristic dimensions, clinically tested, obtained FDA approval of the "new" product, receive another 14 years of data and approval exclusivity, promote it aggressively with doctors and patients (referred to as *converting the market*),²⁵ and effectively extend the monopoly protection on the original product from 29 to 43 years!²⁶ And then BioBrand could tack on another 14 years if it introduced another minor, approved modification in year 43. In the drug world, brand companies have, in such situations, substantially diminished the market for the previous-generation products when they launch a new generation. They do so by converting prescriptions to the new product. Hence, upon approval, the previous-generation generic product has little or no market potential.

Brand companies can, and routinely do, make relatively minor changes to their existing products in order to restart their monopoly-protection clocks.

An effective statutory anti-evergreening provision in biologics would award full monopoly protection only for the discovery and marketing of a new protein. Minor modifications of new proteins should receive either no monopoly protection or very limited protection. Unfortunately, none of the proposed generic biologics bills incorporates any restrictions on evergreening. Instead, they contain vague language about restricting exclusivity provisions to the "previous licensed reference product," without ensuring that what's defined to be the previous licensed reference product is, in fact, the underlying amino acid sequence of the new protein and nothing more.

21 It's easy for even excellent economists to fail to scale costs by revenues. In his June 2007 Duke University Department of Economics working paper titled "Data Exclusivity for New Biologics Entities, Henry Grabowski incorrectly states, "From the standpoint of economic theory, industries where the R&D process is costly and risky need longer exclusivity periods to realize innovation benefits, compared to those industries where innovation is easier and less costly."

22 Henry Grabowski & John Vernon, *Effective Patent Life in Pharmaceuticals*, 19 (Vt) J. Tech. Mgmt. 98 (2000).

23 It's also easy even for excellent economists to confuse diversifiable with aggregate risk. See note 11.

24 The publishing industry doesn't appear in the table because its cost of capital, which is only 7 percent above the average, is below that of biotech. Publishing is another example of an industry in which the chances of success of any given book or other product are very low, yet its overall risk is moderate.

25 Using advertising to transform the old purple-colored Pilsener into the "New Purple Pill" Pilsener is viewed as the classic example of converting the market.

26 Note that patents and exclusivity are different routes to monopoly protection. Minor modifications in medicines need not result in any new patents, yet may still be approved by the FDA as a new product and, therefore, qualify for data as well as approval exclusivity.

The Hatch-Waxman Act — A Balanced Template for Success

The Hatch-Waxman Act provides an excellent guide to establishing a balanced policy with respect to generic biologics. The Act gave the brand and generic companies less than they wanted, but more than they might have expected. The brand companies were forced to confront intense generic competition once their monopoly was finally terminated. In exchange, they received longer monopoly protection. The generics were forced to wait longer to compete, but benefited from an accelerated FDA approval process.

As indicated, the extension of monopoly protection was accomplished via the Act's patent restoration, data exclusivity, approval exclusivity, and ANDA stay provisions. According to the Congressional Budget Office, these and other features of the Act increased the average length of marketing exclusivity by 2.5 years — roughly a 25 percent increase, on average, in the prevailing duration of marketing exclusivity.²⁷ Duke University economists Henry Grabowski and Margaret Kyle report that marketing exclusivity in pharmaceuticals now generally ranges from 12 to 15 years.²⁸

The Hatch-Waxman Act provides an excellent guide to establishing a balanced policy with respect to generic biologics. The Act gave the brand and generic companies less than they wanted, but more than they might have expected.

Gaining access to a market from which they had formerly been excluded (albeit 2.5 years later than they would have preferred) has been a major incentive for generic pharmaceutical companies. Generics, including generics produced by brand companies, now account for two-thirds of the nearly 4 billion U.S. prescriptions being filled each year. This is remarkable given that the generics' prescription share was only 19 percent in 1984 when Hatch-Waxman was passed.²⁹

Generics have achieved this market penetration by offering medically equivalent products at dramatically lower cost. This competition has spurred further innovation. This brings us to Hatch-Waxman's real winner — the American public, which is now able to purchase large numbers of medications at close to their marginal production costs while also benefiting from newly innovated products. In 2007, the sales-weighted discount off

the brand price of the top 100 (ranked by number of prescriptions) generic drugs was 29.0 percent. This is just the average discount. A total of 22 percent of generics are now offering discounts of 40–60 percent, and 20 percent are offering discounts above 60 percent.³⁰

Hatch-Waxman provides four years of data exclusivity, but these four years do not generally preclude generics from reaching market on time. To see this, consider a new chemical medication that receives FDA approval 12 years after initial patent application. Its data exclusivity clock will run out 16 years after initial patent application (i.e., four years after FDA approval). According to table 1, this is still seven years before a generic is able to come to market. Hence, the generic company has seven years to file for and receive FDA ANDA approval.

This example illustrates an important point. Hatch-Waxman's exclusivity provisions, because they are of an appropriate duration, do not lengthen monopoly protection except in extreme cases that FDA approval comes very late — 19 or 20 years — after initial patent application. The real source of Hatch-Waxman's expansion of monopoly protection is patent restoration.³¹

Competition Stimulates Invention

Hatch-Waxman's success did not come at the price of innovation. On the contrary, the legislation appears to have accelerated innovation. Figure 1 shows that research and development in pharmaceuticals, measured relative to sales, increased dramatically in the years after 1984. R&D is now running between 16 percent and 18 percent of sales, on an annual basis, compared with 8–10 percent of sales prior to Hatch-Waxman.

Figures 2 and 3 provide complementary evidence about the acceleration of invention post Hatch-Waxman. Figure 2 shows that the number of new drug patents issued by the U.S. Patent Office rose dramatically after 1984 and, indeed, has exceeded the pre-1984 levels in each year since the Act was promulgated.

Figure 3 reports the average annual number of FDA approvals of new chemical entities (NCEs) for the periods 1973–1983, 1984–1993, and 1994–2007. The figure shows dramatic increases in NCE approvals subsequent to Hatch-Waxman's 1984 passage. NCE approvals increased by one-third in the decade following the bill's passage. Since 1994, NCEs have been coming at twice the rate observed before Hatch-Waxman.

²⁷ Congressional Budget Office, <http://www.cbo.gov/showdoc.cfm?id=656&sequence=1>.

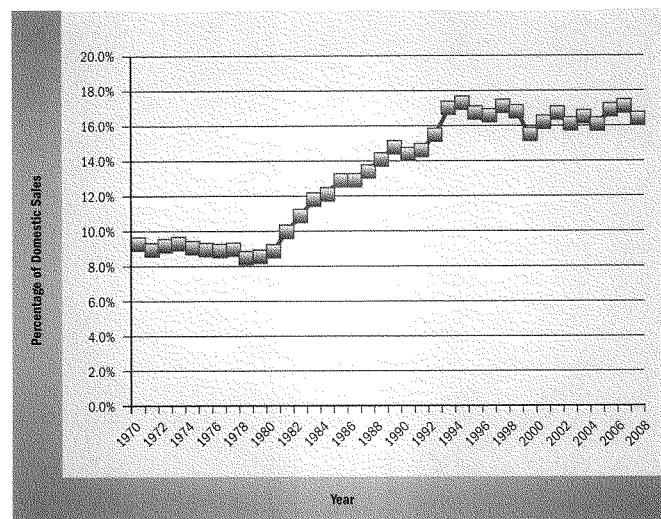
²⁸ Grabowski, Henry G. and Margaret Kyle, "Generic Competition and Market Exclusivity Periods in Pharmaceuticals," *Managerial and Decision Economics*, 28, 491–502, 2007, p. 498.

²⁹ The Congressional Budget Office, "How Increased Competition from Generic Drugs Has Affected Prices and Returns in the Pharmaceutical Industry," July 1998, p. ix.

³⁰ Author's calculations; see note 12.

³¹ Hatch-Waxman's exclusivity provisions are not, however, without teeth. They prevent competitors from challenging patents for four years after FDA approval and from bringing a competitive product to market for five years from FDA approval in the cases that the patent challenge is successful.

Figure 1: Pharmaceutical R&D as a Share of Sales: 1970-2007



Source: PHRMA 2008 Profile.

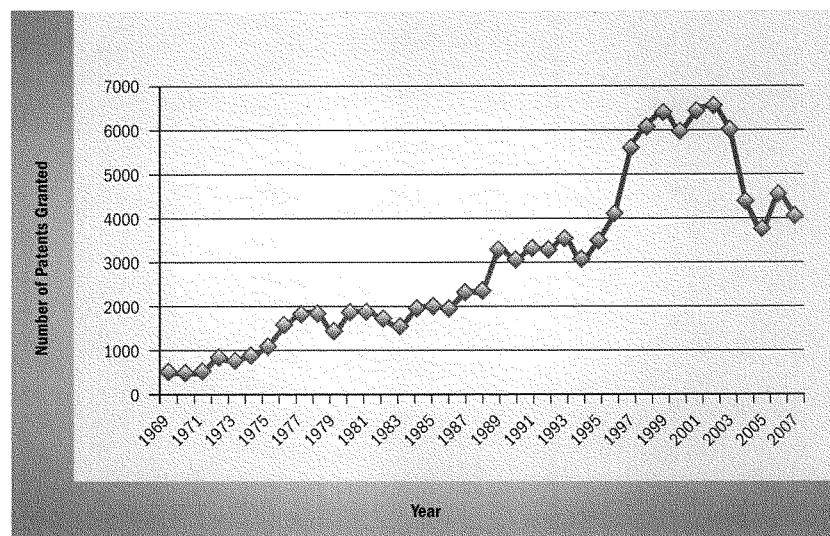
The fact that Hatch-Waxman did not deter the brand companies from investigating new drugs and bringing them to market is not surprising. The average extra two-and-a-half years of marketing exclusivity provided the brand companies more time to recoup their investments. In addition, the four years of data exclusivity and one year of approval exclusivity afforded brand companies five years during which they could market their FDA-approved products without having to contend with competing products arising from legitimate patent challenges.

These points notwithstanding, if Hatch-Waxman did, on balance, reduce the profitability of developing new drugs, its effects were surely modest and were offset by other factors. Such factors include a shift toward more reliance on medication in treating illness, increasing demand for medications from an aging society, increasing international demand due to rising incomes abroad, etc.

Evidence supporting this view of at most a minor impact of Hatch-Waxman comes from a highly detailed 1998 Congressional Budget Office study, which states: "For all drugs, on average, the increase in generic sales since 1984 has probably not reduced expected returns below the average capitalized costs of R&D. On the margin, however, it is possible that a few drugs that were barely profitable to develop before may no longer be so now."³² In reaching this conclusion, the CBO pointed out that the distribution of revenues from new drug discoveries is a highly skewed business, with the successful "blockbuster" drugs generating billions of dollars in sales years before any competition from generic companies comes into play.

Brand companies have also been able to recoup some of the losses arising from generic competition by marketing their brand drugs as generics. In fact, one in every six generic prescriptions is currently being filled with a brand generic.³³

³² Congressional Budget Office, op. cit., p. 28.
³³ Author's calculation based on IMS Health data.

Figure 2: Utility Patent Grants for Drug, Bio-Affecting, and Body-Treating Compositions, 1969–2007

Source: http://www.uspto.gov/web/offices/ac/ido/oeip/taf/becasga/424_tsc.htm

*The recent decline in new drug patent grants between 2002 and 2007 may reflect an overburdened PTO. For example, according to Annual Performance and Accountability Reports issued by the PTO between 2002 and 2007, filings of patent applications have increased from 353,000 in 2002 to 467,000 in 2007. Total patents pending have increased from 636,000 (2002) to 1.12 million (2007). Lastly, in the Biotechnology and Organic Chemistry Section (Tech Center 1600), pendency has increased from 27.3 months (2002) to 34.3 months (2007).

It's also important to note that although generic drugs now account for the bulk of all prescriptions, they continue to account for only a small minority of all sales. As they did back in 1984, the brand companies garner the lion's share of all pharmaceutical revenue. The brand companies' revenue share is currently 84 percent.³⁴ This revenue, by the way, is now running close to a quarter of a trillion dollars each year.³⁵ Thus, brand drug companies remain hugely profitable, with the average price of a brand drug exceeding that of a generic by a factor of roughly four.³⁶

A final point is that Hatch-Waxman surely lit a fire under the brand companies. It's one thing knowing you have an indefinite monopoly on the development, production, and sale of a medication. It's another thing to know that every year of delay in getting to market means one fewer year during which you are likely to collect monopoly rents on your invention. As table 2's third column documents, Hatch-Waxman sent this message loud and clear to the brand companies.

The Economic Case for Biogenics

This final section briefly discusses the potential cost saving and welfare gains from fostering a biogenics industry. I then review some of the relevant economics literature on monopoly protection, making the points that a) innovation is an ongoing process that can be seriously undermined by excessive protection, b) excessive protection can actually reduce incentives to innovate, and c) excessive protection comes at a considerable price in terms of economic efficiency.

Potential Cost Savings from Biogenics

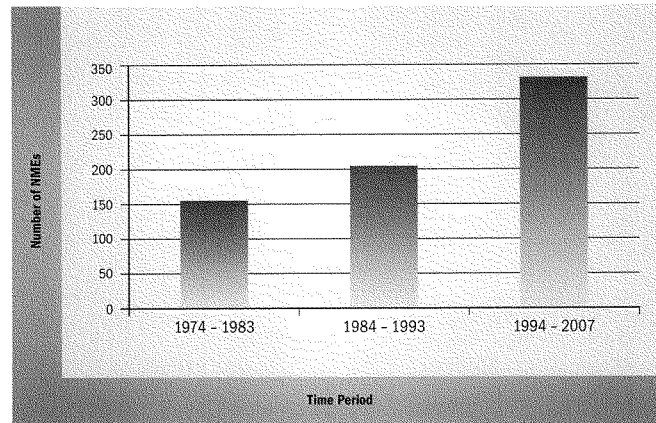
Recent research suggests such an industry would save the American public at least \$25 billion and as much as \$108 billion over the next decade and greater sums thereafter from biogenics leg-

34 IMS Health, "IMS National Prescription Audit Plus, National Sales Perspectives," December 2007.

35 Generic Pharmaceutical Association, *Statistics: Our Industry*, February 2007.

36 *Ibid.*, *FAQs Generics: Lower Cost*, February 2007.

Figure 3: FDA Approvals of New Molecular Entities, 1974–2007



Source (for both) <http://www.fda.gov/cder/dr/da.htm>

isolation that properly limits the duration of monopoly protection.³⁷

Numbers of this magnitude are hard to translate into their personal welfare impact. So take Remicade, which is used to treat arthritis and Crohn's disease. For those with severe arthritis, Remicade infusions can mean the difference between walking or not; and for those with advanced Crohn's, the infusions can literally mean the difference between life and death. That's the very good news. The bad news is that taking this miracle drug can cost over \$20,000 per year.³⁸ Costs of this magnitude are obviously prohibitive for the roughly 50 million Americans with no health insurance as well as the tens of millions of other Americans who either have no prescription drug coverage or face very high prescription co-pays.³⁹

Reducing the Costs of Biologics Limits Biologics Expenditure Risk

Another economic argument for limiting monopoly protection to biologics involves risk. Even those with excellent prescription drug insurance need to worry about the risk of having to directly pay the high costs of biologics. Why? Because being insured today doesn't guarantee being insured tomorrow. Moreover, as *The New York Times* recently reported, health insurance plans with prescription drug coverage are beginning to charge very high co-pays for biologics — usually 20–33 percent. These charges can cost insured patients tens of thousands of dollars a year.⁴⁰ This includes the roughly 33 million elderly Americans on Medicare. A full 86 percent of Medicare Part D prescription drug insurance

37. <http://www.cbo.gov/ftpdocs/94xx/doc9496/s11095.pdf> and Shapiro, Robert J. "The Potential American Market for Generic Biological Treatments and the Associated Cost Savings," *www.imimed.com*, February 2008. Shapiro's cost savings estimate is much higher than CBO's because he incorporates expanded demand in his analysis. The expansion in demand comes from two sources — more consumption of biologics by those now using biologics and the initiation of use of biologics by those now priced out of the market.

38. Purvis, Leigh and Lew Fucker, AARP Public Policy Institute, May 2007. [39. Lowering the costs of biologics directly benefits those using the drugs, but there is also a real benefit to the friends and relatives of those helped by these new medicines. Economists refer to a situation in which person's welfare depends on his own health and consumption or goods and services as well as on person's welfare as one subject to externalities. There are clear and obvious externalities when it comes to improving public health because the "public" when not vaccinated, is often someone to whom we are very close. Remarkably, the economic value of these externalities is entirely ignored when it comes to weighing the costs of granting monopoly protection against the gains. The value could be considerable. Suppose, for example, that each person who is directly helped by having access to a low-cost biologic has 10 close friends or relatives who are indirectly helped. Also suppose that the average value of the external benefit is one-tenth the value to the patient herself. In this case, the savings from low-cost biologics would be double those estimated.](http://64.233.169.104/search?q=cashe%20to%20the%20www.terrific.org/actives_alerts/alerts/2007_06_09/biologics_top_20_e_and_a.pdf&btnG=Go+top+biologic+products&btnG=Go+to+chicago+359&btnG=Remicade+is+actually+expensive+compared+with+some+biologics.+Humira,+which+treats+breast+cancer+runs+$124,000+per+year.+Avelin,+which+treats+colorectal+cancer,+costs+$60,000+annually,+and+Avonex,+which+treats+multiple+sclerosis,+is+valued+at+$4,000+per+year.+Twelve+of+the+top+20+biologics+now+on+the+market+have+an+average+cost+per+year+exceeding+$10,000.+Sixteen+have+an+annual+average+cost+exceeding+$5,000.+See+Purvis+and+Fucker+(2007),+pp.+06.</p>
</div>
<div data-bbox=)

40. Goletta, Gina. "Co-Payments Go Way Up for Drugs with High Prices," *The New York Times*, April 14, 2008.

plans are now charging 20–30 percent co-pays for expensive biologics.⁴¹ Another example of the risk of paying for biologics involves diabetes. Hundreds of thousands of Americans with diabetes, many of whom have prescription drug coverage, are now spending upwards of \$1,000 per month to cover the costs of insulin.⁴²

Our exposure to the risk of high-cost biologics is not limited to our own medical needs. If our relatives or friends end up facing huge, uninsured bills for biologics, we'll be asked for financial assistance or feel the need to provide such assistance. All of these factors are playing on the minds of Americans on a daily basis. According to Deloitte's 2008 *Survey of Health Care Consumers*, 93 percent of American households say they are unprepared for their future healthcare needs. This uncertainty has a cost that economists are well versed in measuring. They do so by determining how much households would be willing to pay to avoid the risk entirely. Although no one has done such a measurement for healthcare expenditure risk in general, let alone biologics per se, the following speculative measurement suggests the potential magnitude of the biologic cost risk.

In fact, each innovation is part of a chain. Today's innovation cannot proceed if yesterday's is not accessible. And tomorrow's innovation must wait until today's innovation is available for use.

Assume there are 100 million Americans who are uninsured either directly or indirectly (via their uninsured relatives' or friends' exposures) for the costs of biologics and that, on average, insurance against these costs is worth \$100 per person. In this case, eliminating this risk would be worth \$10 billion annually.

Now lowering the cost of biologics is not the same as providing insurance against these costs, but it does provide some perspective on the value to American households of less expensive biologics. This value, to repeat, is not simply in reducing expected outlays, including those coming in the form of higher co-pays and prescription drug insurance premiums. It's also in reducing the risk of unaffordable expenditures on biologic medicines.

Limiting Monopoly Protection to Stimulate Innovation

The importance of successive rounds of innovation — of each innovation building on, but also undermining the monopoly position of the prior round⁴³ — was dubbed *creative destruction* by the father of growth theory, Joseph Schumpeter.⁴⁴ According to Schumpeter, innovation is the engine of growth, and it's not pretty. Entrepreneurs must be able to compete and destroy or they will not create.

In Schumpeter's words, "Economic progress, in capitalist society, means turmoil. [What counts is] competition from the new commodity, the new technology, the new source of supply, the new type of organization... competition which... strikes not at the margins of the profits and the outputs of the existing firms, but at their foundations and their very lives."

Paul Romer, today's leading theorist of economic growth, emphasizes the self-propelled nature of growth — that growth feeds upon itself. "We consistently fail to grasp how many ideas remain to be discovered. Possibilities do not add up. They multiply!"⁴⁵

Sandwiched between Schumpeter and Romer is the past century's third great student of economic growth, Nobel laureate Robert Solow. Solow developed *growth accounting* and showed that innovation (better technology) is a major source of U.S. economic growth.

In fact, each innovation is part of a chain. Today's innovation cannot proceed if yesterday's is not accessible. And tomorrow's innovation must wait until today's innovation is available for use. Moreover, if the current length of monopoly protection suffices to incentivize today's innovation, extending the length of protection will do nothing to increase current innovation. Instead, it will simply delay future innovation with the economy, over time, falling further and further behind with respect to the level of technology it would otherwise have available.

Economists have modeled this process, conceptualizing innovation in a number of different ways. Andrew Horowitz and Edwin Lia wrote a classic paper in 1996, for example, in which they view innovation as moving up a product quality ladder.⁴⁶ Higher rungs on the ladder entail better technology and higher quality products. The innovator in their model, which need not be the same person or company through time,⁴⁷ can be viewed as holding the top

41 <http://www.cruitchannels.net/2008/04/tier-4-co-pays-and-pharmacy-prices.html>.

42 Saul, Stephanie. "Bridging of Insulin's Cost, States Push for Generics," *The New York Times*, January 11, 2007. A biologic version of insulin was extracted in the early 1980s; its most effective form has yet to face competition from generic manufacturers.

43 Jorgenson, Dale. "Accounting for Growth in the Information Age," provides a careful empirical analysis available of technology's contribution to U.S. economic growth.

44 Schumpeter, Joseph. *Capitalism, Socialism, and Democracy*. New York, N.Y.: Harper, 1942.

45 <http://www.econlib.org/library/Enc/EconomicGrowth.html>

46 Horowitz, Andrew W. and Edwin L.C. Lia. "Patent Length and the Rate of Innovation," *International Economic Review*, 37 (4), 1996, pp. 785–801. The ladder model for innovation was originally developed by Gene Grossman and Elhanan Helpman in chapter 4 of their book, *Innovation and Growth in the Global Economy*. Cambridge, Mass.: MIT Press, 1992.

47 The current innovator is indifferent between maintaining his company or selling it (his ladder position) to a competitor who would have the same competition-spurred incentive to innovate.

position on the ladder with generics moving up from below. The closer the generics get, the more competition the current innovator faces. This gives the current innovator an incentive to move to yet a higher position on the ladder. Moving up the ladder is innovation, and the more rungs the innovator (or replacement innovator) climbs over a given period of time, the higher the rate of innovation.

Patent length in the model corresponds to the amount of time the government keeps the generics from using the latest technology — moving up the ladder to where the prior innovators have been. Once the current patent expires, the generic can move up. But when he does, he finds that the top-rung innovator has innovated to an even higher rung, the position of which is temporarily protected by a new patent.

This is not a model of evergreening. Each time the top-rung innovator company innovates, it represents a true improvement in technology — one that comes at a real cost to the company. But it's only the threat of competition that keeps the top-rung innovator (the near monopolist) innovating. And setting the patent length correctly is critical. As the authors point out, "Patent length either too short, or too long, will weaken innovative incentives." In particular, patent length that's too long will lead to more innovation when innovation occurs (the top-rung company will move up more rungs when it realizes it has to innovate to stay ahead because its patent is expiring), but to less frequent innovation. In the extreme, making the patent indefinite kills off innovation entirely; in this case, the top-rung company faces no competitive pressure and would compete only against itself by incurring the cost of inventing a better product.

Another classic paper on patent policy is Nancy Gallini's (1992) *Rand Journal* article.⁴⁸ Gallini's model lets competitors invent around incumbents, but at a cost. If patent length is set too long, competitors realize that they'll not be able to use existing knowledge in a timely manner and that the only way they can compete is to come up with their own invention. Under these circumstances, this makes private sense, but it also makes social non-sense for the same reason that it makes no sense to re-invent the wheel. Knowledge that's been acquired at a cost and that can be conveyed at zero cost is knowledge that should be used.

Gallini's paper, in its own way, gets at the cost of patent races alluded to above. Invention that can be monopolized even for a finite period of time represents a prize worth fighting for. But if only one party can win or, in Gallini's case, if multiple parties can win, but not fully, there can be too much effort put into invention. Again, what's privately optimal can be socially undesirable.

The classic example of such *rent seeking* is referred to as *the Tragedy of the Commons*. In this case, there is a common field that shepherds can use to graze their flocks. But since no one owns the commons or cares about the degree to which the grazing of his sheep limits the grazing of other people's sheep, we end

Once the current patent expires, the generic can move up. But when he does, he finds that the top-rung innovator has innovated to an even higher rung, the position of which is temporarily protected by a new patent.

up with overgrazing. In the extreme, there can be so much overgrazing that no one benefits from the commons — a real tragedy. Similarly, if extending patent length too long makes the prize of coming up with the winning invention so great, far too many would-be inventors will abandon their other pursuits and try to strike it rich. The resulting gold rush can lead to collective (social) costs that entirely wipe out the social benefit from the invention.⁴⁹

Gallini's paper provides yet another deep insight into the problem of excessively long monopoly protection. She points out that extending patent life beyond the socially optimal length may actually be counterproductive in terms of incentivizing innovators to invent. The reason is that an innovator, call her X, will realize that if she wins the patent race, her competitors will know that waiting until her patent expires is waiting too long and that the only way to play is to innovate around her patent. In thinking this through, X will realize that having longer life on a patent that others are going to invent around is like having a very short patent that others will not invent around; i.e., it's like having little incentive to invent in the first place. Gallini summarizes this point by stating "Extending patent life ... may not provide the inventor with increased incentive to research or patent the innovation."

Limiting Monopoly Protection to Increase Economic Efficiency

If less monopoly protection can be more when it comes to stimulating invention, the same holds true when it comes to improving economic efficiency. In his fundamental paper on optimal patent life, William Nordhaus argues that "the optimal life for drastic process inventions seems to be very small, in the order of one-tenth of the actual life of patents. The reason for the very

48. Gallini, Nancy L., "Patent Policy and Costly Imitation," *Rand Journal of Economics*, 23 (1), Spring 1992.

49. Philip Aghion and Peter Howitt in their 1992 *Econometrica* 60, 2, March 1992, pp. 323–51 paper titled "A Model of Growth through Creative Destruction" refer to the waste of resources in patent races as "business stealing."

small (optimal) life seems to be that drastic inventions are very important inventions and thus have a great deal of potential dead-weight loss if they have long life.⁵⁰

Drastic inventions refer here to inventions that lead to major reductions in the prices facing consumers once patent protection terminates. But the fact that the true economic cost for consumers of consuming a product is quite low means they should be consuming a lot of it. But with extended monopoly protection this doesn't happen, or at least doesn't happen for a very long time. The resulting consumer loss in welfare is called a deadweight loss.

Glenn Loury reaches a similar conclusion to Nordhaus, but in a more realistic setting in which the overall economy's conditions change when patent policy is modified. Loury states, "Social welfare can be maximized by appropriately limiting entry and firm investments with licensing fees and finite patent life."⁵¹

Conclusion

Biologic medications hold enormous promise for improving Americans' health and well-being. Fulfilling that promise requires making sure that all Americans are able to access these medications at affordable prices within a reasonable period of time from their discovery. It also requires ensuring that tomorrow's biological breakthroughs are able to build on today's.

Biologic medications hold enormous promise for improving Americans' health and well being. Fulfilling that promise requires ensuring that all Americans are able to access these medications at affordable prices within a reasonable period of time from their discovery.

Legislation now pending in Congress offers hope to millions of Americans that more affordable versions of biologic medications will soon become available through a competitive marketplace. But exclusivity provisions in three of the four main biogenerics bills significantly undermine the legislation's objectives. These provisions constitute uncontested grants of monopoly rights by government fiat — something that runs far afield of traditional U.S. patent policy. The provisions would substantially extend the duration of monopoly protection of brand biologic medicines and, thereby, materially delay the arrival of low-cost generic alternatives. These conveyances of exclusive marketing rights not only exclude competing biologic companies from entering the market

with low-cost alternatives for extended periods of time. They also exclude other innovators from building, in a timely manner, on the stock of prior knowledge, much of which was accumulated at public expense. These bills also fail to anticipate and prevent evergreening under which brand companies can obtain repeated periods of exclusivity and monopolize biologic medicines essentially indefinitely.

New medications that alleviate or cure terrible disease are such remarkable gifts to humankind that we must continue to appropriately reward true innovation in this field. But the new drugs of today are not those of tomorrow. And today's inventors are generally not tomorrow's. The reason is clear. Today's inventors have strong incentives to protect their discoveries, not make new ones whose arrival on the market would undermine their existing profits and market share. And, as numerous papers in the economics literature on invention and monopoly protection point out, over-extending monopoly protection can easily boomerang. It may do little or nothing to incentivize new discovery and simply delay when the next discovery comes on board. *In this case, providing greater incentive to innovate leads to less, not more, innovation over time.*

Without question, the American biologics drug industry is a golden goose, which is advancing the healthcare of our citizens. The presumption of many is that feeding this goose more and more will lead it to produce an ever-greater number of eggs at a faster pace. But doing so is very dangerous. After all, why should the goose produce as much when it has less incentive, and why should anyone look for a better goose if the current one cannot be displaced?

Fortunately, we don't need to guess how much to feed the biologics goose. Its chemical cousin — the pharmaceutical goose — is, from all appearances, essentially identical in its diet and response to incentives. What works for the pharmaceutical goose will surely work for the biologics one. And what works for the pharmaceutical goose in promoting and protecting innovation is the Hatch-Waxman legislation — a bill whose exclusivity provisions are sufficiently balanced as to not over-extend the duration of monopoly protection.

Close to a quarter of a century's experience speaks clearly. Hatch-Waxman provides its goose with a balanced diet — one that provides brand companies with appropriate incentives to develop and market their products, one that permits competitors to lower pharmaceutical prices to the public in a timely manner, and one that keeps new pharmaceutical discoveries coming at a rapid pace.

50 Nordhaus, William O., "The Optimal Life of a Patent," Cowles Foundation paper no. 2421, Yale University November 27, 1987.
51 Loury, Glenn C., "Market Structure and Innovation," *The Quarterly Journal of Economics*, 93, 3, August 1979, 395-410.

Appendix: Industry Beta and Risk-Adjusted Cost of Equity

Industry Name	Firms in Sample	Beta	Beta/ Mean Beta	Cost of Equity	Cost of Equity/ Mean Cost of Equity
Market	7364	1.24	1.00	10.8%	1.00
Semiconductor	138	2.59	2.09	20.4%	1.89
Semiconductor Equipment	16	2.51	2.02	19.8%	1.83
Wireless Networking	74	2.2	1.77	17.6%	1.63
E-Commerce	56	2.08	1.68	16.8%	1.55
Entertainment Tech.	38	2.06	1.66	16.6%	1.54
Telecom. Equipment	124	1.98	1.60	16.1%	1.49
Internet	266	1.97	1.59	16.0%	1.48
Steel (Integrated)	14	1.97	1.59	16.0%	1.48
Manuf. Housing/RV	18	1.92	1.55	15.6%	1.45
Power	58	1.87	1.51	15.3%	1.41
Computers/Peripherals	144	1.86	1.50	15.2%	1.41
Pharmaceuticals	368	1.78	1.44	14.6%	1.35
Coal	18	1.71	1.38	14.1%	1.31
Steel (General)	26	1.71	1.38	14.1%	1.31
Precision Instrument	103	1.66	1.34	13.8%	1.28
Securities Brokerage	31	1.66	1.34	13.8%	1.28
Homebuilding	36	1.64	1.32	13.6%	1.26
Advertising	40	1.6	1.29	13.4%	1.24
Retail Automotive	16	1.58	1.27	13.2%	1.22
Cable TV	23	1.56	1.26	13.1%	1.21
Computer Software/Svcs.	376	1.56	1.26	13.1%	1.21
Auto & Truck	28	1.54	1.24	12.9%	1.20
Recreation	73	1.54	1.24	12.9%	1.20
Entertainment	93	1.53	1.23	12.9%	1.19
Chemical (Basic)	19	1.52	1.23	12.8%	1.18
Biotechnology	103	1.51	1.22	12.7%	1.18

Source: author's calculations based on betas posted 1/06 by Kenneth Damodaran, NYU Professor of Finance at http://pages.stern.nyu.edu/~damodara/New_Home_Page/datafile/betas.html. Cost of equity is calculated as $.02 + \beta \times (.091 - .02)$, where .02 is the risk-free rate (based on prevailing TIPS yields) and .091 is the average annual real return on large-cap equity calculated from Ibbotson data from 1926 to the present.

ABOUT THE AUTHOR

Laurence J. Kotlikoff is professor of economics at Boston University, research associate of the National Bureau of Economic Research, fellow of the American Academy of Arts and Sciences, fellow of the Econometric Society, and president of Economic Security Planning, Inc., a company specializing in financial planning software. Professor Kotlikoff received his B.A. in economics from the University of Pennsylvania in 1973 and his Ph.D. in economics from Harvard University in 1977. From 1977 through 1983 he served on the faculties of economics of the University of California, Los Angeles and Yale University. In 1981–82 Professor Kotlikoff was a senior economist with the President's Council of Economic Advisers. Professor Kotlikoff has served as a consultant to the International Monetary Fund, the World Bank, the Harvard Institute for International Development, the Organization for Economic Cooperation and Development, the Swedish Ministry of Finance, the Norwegian Ministry of Finance, the Bank of Italy, the Bank of Japan, the Bank of England, the government of Russia, the government of Ukraine, the government of Bolivia, the government of Bulgaria, the Treasury of New Zealand, the Office of Management and Budget, the U.S. Department of Education, the U.S. Department of Labor, the Joint Committee on Taxation, the Commonwealth of Massachusetts, the American Council of Life Insurers, Merrill Lynch, Fidelity Investments, AT&T, AON Corp., and other major U.S. corporations. He has provided expert testimony on numerous occasions to committees of Congress, including the Senate Finance Committee, the House Ways and Means Committee, and the Joint Economic Committee. Professor Kotlikoff is author or co-author of 13 books and hundreds of professional journal articles. His most recent book, co-authored with Scott Burns, is forthcoming with Simon & Schuster and is titled *Spend 'Til the End*. Professor Kotlikoff publishes extensively in newspapers and magazines on issues of deficits, generational accounting, the tax structure, Social Security, Medicare, health reform, pensions, saving, insurance, and personal finance.

Teva USA Government Affairs

444 North Capitol Street NW

Suite 722

Washington, DC 20001

202-220-1380

www.tevadc.com

Biologics in Perspective: The Case for Generic Biologic Drugs

Based on U.S. sales alone, many top selling biologic drugs have recouped their manufacturer's initial investment several times over in the past six years, often within a single year.

Spending on biologic drugs is growing nearly twice as quickly as spending on traditionally-developed "small molecule" drugs.

Overall biologic drug sales reached \$75 billion in 2007¹, and it is estimated that spending on biologics will continue to increase substantially through 2012.²

One factor driving spending on biologics is the lack of a statutory pathway to approve generic, or bio-equivalent, biologic drugs.

Conventional drug products fall under the purview of the Federal Food, Drug, and Cosmetic Act, which has a streamlined process to approve generic drug products. However, the majority of biologics fall under the Public Health Service Act, which does not have an equivalent pathway. Therefore, biologic drug patent holders currently do not face generic competition, even though more than half of the top 20 biologics have either gone off patent or will do so by 2012.³ This leaves manufacturers free to continue charging prices that are considerably higher than the prices of most non-biologic drugs. For example, Avastin, a biologic drug that is used to treat patients with advanced colon, lung or breast cancer, can cost up to \$100,000 per year.⁴

There is near-universal agreement that creating a pathway for generic biologic drugs would save billions of dollars.⁵

The Medicare Payment Advisory Commission (MedPAC) has clearly stated that an abbreviated biogenerics approval process is urgently needed because the availability of follow-on biologics will lead to increased competition, and that will improve the accuracy of Medicare's payment method and the value of Medicare spending.⁶

Some manufacturers say they must protect their patents because of the costs associated

with biologic drug development. However, based on U.S. sales alone, many top selling biologic drugs have recouped their manufacturer's initial investment several times over in the past six years; often within a single year (see Figure 1).

Between the rapid rise in the number of biologic drugs⁷ and regularly expanding indications for the products that are already on the market⁸, biologics are quickly becoming a common treatment option. Many of the new indications are for conditions that primarily affect older populations, such as cancer, rheumatoid arthritis, and multiple sclerosis. However, given the substantial out-of-pocket costs that can be associated with using biologic drugs, many patients will face impeded access until generic biologic drugs become available.

¹ IMS Health, "IMS Health Reports Global Biotech Sales Grew 12.5 Percent in 2007, Exceeding \$75 Billion," June 17, 2008.

² Express Scripts, "2007 Drug Trend Report," April 2008.

³ E. Ehrlich and E.L. Wright, Biogenerics: What They Are, Why They Are Important, and Their Economic Value to Taxpayers and Consumers, Policy Brief, Citizens Against Government Waste, May 2, 2007.

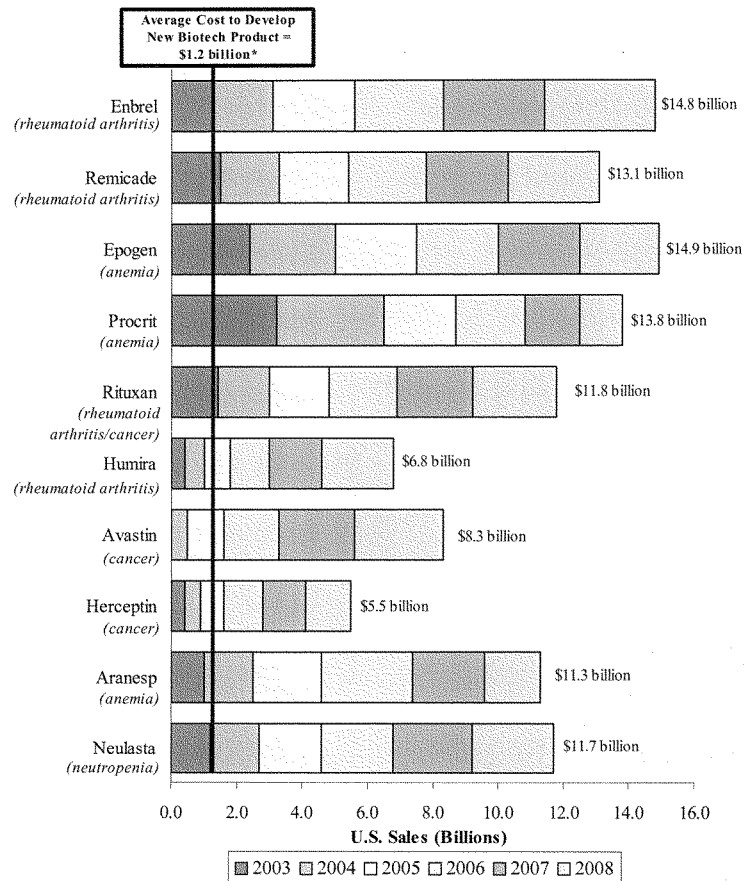
⁴ G. Kolata and A. Pollack, "Costly Cancer Drug Offers Hope, but Also a Dilemma," New York Times, July 6, 2008.

⁵ S. Miller and J. Houts, "Potential Savings of Biogenerics in the United States," Express Scripts, February 2007; A. Ahlstrom et al., "Modeling Federal Cost Savings from Follow-on Biologics," Avalere Health, April 2007; Engel & Novitt, LLP, "Potential Savings That Might Be Realized by the Medicare Program From Enactment of Legislation Such As The Access To Life-Saving Medicine Act (H.R. 6257/S. 4016) That Establishes A New cBLA Pathway For Follow-On Biologics," PCMA, January 2, 2007.

⁶ MedPAC, "Report to the Congress, Medicare Payment Policy (Outpatient Dialysis Services)," March 2008.

⁷ There are now more than 250 FDA-approved biologic medicines and more than 300 in development. J. Greenwood, "The Biotechnology Industry Organization," Chain Drug Review, January 5, 2009.

⁸ For example, Avastin, which was approved in 2004, has 23 potential additional indications under development. M. Said, C. A. Brouwers, and P. Tollman, "Continued Development of Approved Biological Drugs," The Boston Consulting Group, White Paper, December 2007.

Figure 1: Annual and Total U.S. Sales for Top Selling¹ Biologic Drugs, 2003-2008

* Tufts Center for the Study of Drug Development, Press Release, "The cost to develop new biotech products is estimated to average \$1.2 billion," November 9, 2006.

Note: Numbers reflect annual sales in the United States; total (global) annual sales are considerably higher.

Source: AARP Public Policy Institute analysis of manufacturer financial reports and Drugs.com, "Top 200 Drugs for 2003 by U.S. Sales" and "Top 200 Drugs for 2004 by U.S. Sales." Available on the Web at: <http://www.drugs.com/>.

¹ Based on La Merie, "Top 20 Biologics 2008 (global sales)," March 2009.

Fact Sheet 155, May 2009

Written by Leigh Purvis
AARP Public Policy Institute
601 E St., NW, Washington, DC 20049
www.aarp.org/ppi
202-434-3890, ppi@aarp.org
© 2009, AARP
Reprinting with permission only.