

**DATES:** Although you can comment on any guidance at any time (see 21 CFR 10.115(g)(5)), to ensure that the Agency considers your comment of this draft guidance before it begins work on the final version of the guidance, submit either electronic or written comments on the draft guidance by August 9, 2011.

**ADDRESSES:** Submit written requests for single copies of the draft guidance document entitled "Establishing the Performance Characteristics of In Vitro Diagnostic Devices for *Chlamydia Trachomatis* and/or *Neisseria Gonorrhoeae*: Screening and Diagnostic Testing" to the Division of Small Manufacturers, International, and Consumer Assistance, Center for Devices and Radiological Health, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 66, rm. 4613, Silver Spring, MD 20993-0002. Send one self-addressed adhesive label to assist that office in processing your request, or fax your request to 301-847-8149. See the **SUPPLEMENTARY INFORMATION** section for information on electronic access to the guidance.

Submit electronic comments on the draft guidance to <http://www.regulations.gov>. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Identify comments with the docket number found in brackets in the heading of this document.

**FOR FURTHER INFORMATION CONTACT:** Kathleen Whitaker, Center for Devices and Radiological Health, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 66, rm. 5500, Silver Spring, MD 20993-0002, 301-796-6208.

**SUPPLEMENTARY INFORMATION:**

**I. Background**

FDA is issuing this draft guidance to provide industry and Agency staff with recommendations for studies to establish the analytical and clinical performance of IVDs intended for *C. trachomatis* and/or *N. gonorrhoeae* screening and diagnostic testing using nucleic acid based assays. These devices are used to aid in the diagnosis of urogenital *C. trachomatis* and *N. gonorrhoeae* infection. They include devices that detect one specific organism, as well as devices that may detect both organisms with or without further differentiation.

This draft guidance provides detailed information on the types of studies FDA recommends to support class I and class II premarket submissions for these devices. The draft guidance includes a list of *C. trachomatis* and *N.*

*gonorrhoeae* strains recommended for analytical sensitivity studies and a list of micro-organisms recommended for analytical specificity studies. This document also addresses recommendations for fulfilling labeling requirements applicable to all in vitro diagnostic devices intended to screen for, or aid in the diagnosis of, *C. trachomatis* and/or *N. gonorrhoeae* directly from human specimens.

This document is limited to studies intended to establish the performance characteristics of devices that detect chlamydial and/or gonococcal nucleic acid. It does not address detection of serological response from the host to bacterial antigens, nor does it address establishing performance of non-chlamydial or non-gonococcal components of non-analyte or multiplex devices.

**II. Significance of Guidance**

This draft guidance is being issued consistent with FDA's good guidance practices regulation (21 CFR 10.115). The draft guidance, when finalized, will represent the Agency's current thinking on establishing the performance characteristics of in vitro diagnostic devices for *C. trachomatis* and/or *N. gonorrhoeae* screening and diagnostic testing. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute and regulations.

**III. Electronic Access**

Persons interested in obtaining a copy of the draft guidance may do so by using the Internet. A search capability for all CDRH guidance documents is available at <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/default.htm>. Guidance documents are also available at <http://www.regulations.gov>. To receive "Establishing the Performance Characteristics of In Vitro Diagnostic Devices for *Chlamydia Trachomatis* and/or *Neisseria Gonorrhoeae*: Screening and Diagnostic Testing," you may either send an e-mail request to [dsmica@fda.hhs.gov](mailto:dsmica@fda.hhs.gov) to receive an electronic copy of the document or send a fax request to 301-847-8149 to receive a hard copy. Please use the document number 1733 to identify the guidance you are requesting.

**IV. Paperwork Reduction Act of 1995**

This draft guidance refers to previously approved collections of information found in FDA regulations and guidance documents. These

collections of information are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501-3520). The collections of information in 21 CFR part 807, subpart E have been approved under OMB control number 0910-0120; the collections of information in 21 CFR part 812 have been approved under OMB control number 0910-0078; the collections of information in 21 CFR parts 56.115 have been approved under OMB control number 0910-0130; and the collections of information in 21 CFR part 801 and 21 CFR 809.10 have been approved under OMB control number 0910-0485.

**V. Comments**

Interested persons may submit to the Division of Dockets Management (see **ADDRESSES**) either electronic or written comments regarding this document. It is only necessary to send one set of comments. It is no longer necessary to send two copies of mailed comments. Identify comments with the docket number found in brackets in the heading of this document. Received comments may be seen in the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday.

Dated: May 6, 2011.

**Nancy K. Stade,**

*Deputy Director for Policy, Center for Devices and Radiological Health.*

[FR Doc. 2011-11532 Filed 5-10-11; 8:45 am]

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**DEPARTMENT OF HEALTH AND HUMAN SERVICES**

**Food and Drug Administration**

[Docket No. FDA-2010-N-0621]

**Proposal To Withdraw Approval for the Breast Cancer Indication for Bevacizumab; Hearing**

**AGENCY:** Food and Drug Administration, HHS.

**ACTION:** Notice of hearing.

**SUMMARY:** The Food and Drug Administration (FDA) is granting a hearing to Genentech, Inc. (Genentech), on the Center for Drug Evaluation and Research's (CDER's) proposal to withdraw approval of the breast cancer indication for bevacizumab (Avastin). Genentech is the sponsor for Avastin. Genentech and CDER are the parties to the hearing. The issues to be discussed and resolved at the hearing relate directly to the statutory and regulatory standard for FDA to withdraw accelerated approval of the metastatic

breast cancer (MBC or breast cancer) indication for Avastin.

**DATES: Date and Time:** The hearing will be held on June 28 and 29, 2011, from 8 a.m. to 5 p.m.

**ADDRESSES:** The hearing will be held at FDA's White Oak Campus, 10903 New Hampshire Ave., Bldg 31, Rm. 1503 (Great Room), Silver Spring, MD 20993.

**FOR FURTHER INFORMATION CONTACT:** Talisha Williams, Office of the Ombudsman, Office of the Commissioner, Food and Drug Administration, 10903 New Hampshire Ave., Silver Spring, MD 20993, 301-796-8530, e-mail: [Talisha.Williams@fda.hhs.gov](mailto:Talisha.Williams@fda.hhs.gov).

**SUPPLEMENTARY INFORMATION:**

**Registration and Requests to Make Oral Presentations:** On June 28, 2011, up to 2 hours of the hearing have been reserved for oral presentations by persons other than the parties.

If you wish to make an oral presentation during the hearing, you must register by submitting an electronic or written request by May 27, 2011, to Talisha Williams (see **FOR FURTHER INFORMATION CONTACT**).

Depending on the number of requests, FDA may not be able to honor all such requests. You must provide your name, title, business affiliation (if applicable), address, telephone and fax numbers, e-mail address, and (if applicable) type of organization you represent (e.g., industry, consumer organization). You also should submit a brief summary of the presentation, including the discussion topic(s) that will be addressed and the approximate time requested for your presentation. We encourage individuals and organizations with common interests to consolidate or coordinate their presentations to allow adequate time for each request for presentation. If there are many requests to present during the 2-hour period, the amount of time that can be allotted to each presenter may be limited to provide an opportunity to as many persons wishing to present as possible. Persons registered to make an oral presentation should check in with Talisha Williams before the hearing. Participants should submit a copy of each presentation to Talisha Williams.

We will file the hearing schedule, indicating the order of presentation and the time allotted to each person, with the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852 and it will be posted on <http://www.regulations.gov>. We will mail, e-mail, or telephone the schedule to each participant before the hearing. In

anticipation of the hearing presentations moving ahead of schedule, participants are encouraged to arrive early to ensure their designated order of presentation. Participants who are not present when called risk forfeiting their scheduled time.

If you need special accommodations due to a disability, please contact Talisha Williams at least 7 days in advance.

**Registration and Requests to Attend the Hearing:** The public hearing is free, but all persons wishing to attend the hearing, who have not registered to make an oral presentation, must register with FDA in advance of the hearing. By May 20, 2011, FDA will post further details regarding the registration process for attendees to its Web site at <http://www.fda.gov>. Beginning May 27, 2011, you will be able to register to attend the hearing via FDA's Web site at <http://www.fda.gov>. Space in the Great Room, where the hearing is to be held, will be limited to 300 persons from the general public, and thus registration will be first-come, first-served.

**Web cast:** The hearing will also be available to be viewed online via a Web cast. Availability of the Web cast to the public will also be limited to a certain number of persons, and registration will be required to access the Web cast. By May 20, 2011, FDA will post further details regarding the Web cast and the registration process for the Web cast to the Agency's Web site at <http://www.fda.gov>. Beginning May 27, 2011, you will be able to register to access the Web cast via FDA's Web site at <http://www.fda.gov>.

**Comments:** Regardless of participation in the public hearing, interested persons may submit electronic or written comments on CDER's proposal to withdraw approval of the MBC indication. Submit electronic comments to <http://www.regulations.gov>. Submit written comments to the Division of Dockets Management (see **Registration and Requests to Make Oral Presentations**). Comments must be submitted by July 14, 2011. It is only necessary to send one set of comments. It is no longer necessary to send two copies of mailed comments. Identify comments with the docket number found in brackets in the heading of this document. Submission of comments prior to the meeting is strongly encouraged.

All documents filed or posted in this matter are available for public review under Docket No. FDA-2010-N-0621 in the Division of Dockets Management (see **Registration and Requests to Make Oral Presentations**) between 9 a.m. and 4 p.m., Monday through Friday. Persons

with access to the Internet may obtain documents at <http://www.regulations.gov>.

## I. Background

Section 506 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 356), which was added to the statute with the passage of the Food and Drug Modernization Act of 1997, provides for the accelerated, or fast track, approval of a drug product when FDA determines that the " \* \* \* product has an effect on a clinical endpoint or on a surrogate endpoint that is reasonably likely to predict clinical benefit" (section 506(b)(1)). Section 506 of the FD&C Act also provides explicit authority for FDA to use expedited procedures to withdraw accelerated approval of a product under certain circumstances.

FDA's regulations regarding the accelerated approval of biological products (§§ 601.40 through 601.46; part 601, subpart E) (21 CFR 601.40 through 601.46; 21 CFR part 601, subpart E) set forth the procedures that FDA uses to withdraw accelerated approval for a biological product. Under § 601.43(b), FDA notifies the sponsor of the biological product of an opportunity for a hearing on a proposal to withdraw approval of the product. FDA conducts such hearings in accordance with the procedures set forth in part 15 (21 CFR part 15), with some specific modifications, including the presence of an advisory committee duly constituted under 21 CFR part 14, which provides advice and recommendations to the Agency (§ 601.43(e)).

On February 22, 2008, under section 506 of the FD&C Act and FDA's implementing regulations for accelerated approval of biological products, CDER approved supplemental biological license application 125085/91 (the sBLA), which was submitted by Genentech. The sBLA sought approval of Avastin for use in combination with the chemotherapy drug paclitaxel for the treatment of patients who have not received chemotherapy for metastatic HER2 negative breast cancer. Consistent with the regulations requiring postmarket studies for accelerated approval (see CFR 601.41 and 601.43), CDER's approval of the MBC indication for Avastin was subject to the requirement that the product be studied further to verify and describe clinical benefit. The two specific ongoing clinical trials identified to verify and describe clinical benefit were: Trial BO17708 (AVADO) (NCT 00333775) and Trial AVF 3694g (RIBBON1) (NCT 00262067). On November 16, 2009, Genentech submitted the results of the AVADO and RIBBON1 trials to CDER.

On December 16, 2010, CDER issued a notice for opportunity for a hearing (NOOH) on a proposal to withdraw approval of the MBC indication for Avastin. The NOOH stated CDER's conclusions that AVADO and RIBBON1 failed to verify clinical benefit with respect to the MBC indication for Avastin and that, because of that failure, the risk/benefit assessment that supported the initial approval of the MBC indication had changed significantly such that Avastin no longer met the safety and effectiveness requirements for continued marketing for that indication. On January 16, 2011, Genentech requested a hearing and submitted the data and information on which it intends to rely at the hearing.

By letter dated February 23, 2011, Karen Midthun (the Presiding Officer), advised the parties that FDA was granting the hearing request and that the Commissioner of Food and Drugs (the Commissioner) had appointed her as presiding officer. The letter stated that, although not required by FDA's regulations (see § 601.43(d)), the Agency would be observing separation of functions for purposes of the hearing. The letter further communicated FDA's conclusion that FDA's regulations require that the Agency's Oncologic Drugs Advisory Committee (ODAC) serve as the advisory committee for the hearing and to provide advice and recommendations to the Commissioner under § 601.43(e)(1). Finally, the Presiding Officer directed Genentech and CDER to submit a joint statement of undisputed facts and disputed issues.

On April 7, 2011, Genentech and CDER submitted a "Joint Statement of Undisputed Facts and Select Issues in Dispute" (Joint Statement). On April 8, 2011, Genentech and CDER submitted separate statements of questions to be presented at the hearing.

## II. Hearing Issues and Process

FDA hereby grants Genentech's request for a hearing under § 601.43 and part 15 on CDER's proposal to withdraw approval of the MBC indication for Avastin.

### A. Issues

The issues to be decided at the hearing relate directly to the statutory and regulatory standard for FDA to withdraw accelerated approval of the MBC indication for Avastin. On April 7, 2011, in response to direction from the Presiding Officer to consult with each other and submit an agreed statement of the issues in dispute in this hearing, counsel for Genentech and CDER reported that they were unable to reach agreement on how to frame the issues to

be resolved. The issues for decision will thus be stated in accordance with the statute and regulations.

The applicable regulation is § 601.43. This regulation was finalized in 1992 (57 FR 58942, December 11, 1992). In 1997, Congress enacted section 506 of the FD&C Act, which sets out criteria for expedited approval and withdrawal of approval of "fast-track products." It is FDA's position that section 506(b) of the FD&C Act, while enacted after the finalization of the regulation, essentially codifies in the statute FDA's accelerated approval regulations. Section 506(b)(3) of the FD&C Act sets out four bases for expedited withdrawal of approval of a product approved under the accelerated procedures. Section 601.43(a) sets out six bases. In this matter, there appears to be agreement that two of the bases will be at issue in this hearing. These two bases appear in both the regulations and the statute.

One basis for withdrawal of approval of a product approved under the accelerated procedures, set out in nearly identical language in § 601.43(a)(1) and section 506(b)(3)(B) of the FD&C Act, is that FDA may withdraw approval if, in the words of the regulation: "A postmarketing clinical study fails to verify clinical benefit", or, in the words of the statute, if: "[A] post-approval study of the fast track product fails to verify clinical benefit of the product."

In this case, the parties agree that "During CDER's review of [the sBLA], Genentech proposed and CDER agreed that the AVADO and RIBBON1 trials could serve as the required trial(s) to verify and describe the clinical benefit" (Joint Statement, paragraph 31). Thus, one ultimate issue in this hearing is:

*Issue 1.* Do the AVADO and RIBBON1 trials fail to verify the clinical benefit of Avastin for the breast cancer indication for which it was approved?

If, after the hearing, the Commissioner concludes that these studies fail to verify the clinical benefit of Avastin for that indication, FDA may withdraw the approval.

CDER also seeks to base the withdrawal of approval on an alternative ground. This ground is set forth in the regulation and in the statute. Section 601.43(a)(6) states that FDA may withdraw approval if: "Other evidence demonstrates that the biological product is not shown to be safe or effective under its conditions of use."

Section 506(b)(3)(C) of the FD&C Act states that withdrawal is authorized if: "[O]ther evidence demonstrates that the fast track product is not safe or effective under the conditions of use."

In this case, the parties have agreed that the FDA-approved prescribing

information for Avastin "is a fair and accurate description of the safety profile of Avastin," and that "[t]he safety data observed in the E2100, AVADO, and RIBBON1 studies were consistent with the safety profile of Avastin described in its approved prescribing information" (Joint Statement, paragraphs 22 and 23). In light of this agreement, the dispute with respect to this issue centers on the effectiveness information for the breast cancer indication, and on the appropriate risk-benefit analysis to be made in light of that information as compared to the agreed risk of the product. Thus, FDA does not anticipate that the hearing will involve any dispute about the safety information in the clinical studies.

The safety profile of Avastin described in its approved prescribing information includes a black box warning concerning gastrointestinal perforation, surgery and wound healing complications, and severe or fatal hemorrhage. Genentech does not state that the use of this drug in the treatment of breast cancer is safe in the abstract. Instead, it states that the drug should be found to be safe because its use provides benefits to patients that outweigh its risks. Applying the standard in the regulation and statute to the facts presented, therefore, the issue for resolution will be:

*Issue 2.A.* Does the available evidence on Avastin demonstrate that the drug has not been shown to be effective for the breast cancer indication for which it was approved?

*Issue 2.B.* Does the available evidence on Avastin demonstrate that the drug has not been shown to be safe for the breast cancer indication for which it was approved, in that Avastin has not been shown to present a clinical benefit that justifies the risks associated with use of the product for this indication?

A third issue is presented by the fact that both section 506(b)(3) of the FD&C Act and § 601.43(a) do not by their terms require the withdrawal of an accelerated approval even if the bases for withdrawal they describe are present. Instead, in each case, the statute and regulation state that FDA "may" withdraw approval in those circumstances. This standard reflects the fact that decisions on withdrawals of approval of products necessarily reflect judgment on FDA's part as to what actions are appropriate to protect the public with respect to approved products, and what uses of those products should be stated on the labels of those products.

Genentech has stated that the "core issue presented in this proceeding [is] whether FDA should maintain or

withdraw the accelerated approval of Avastin for [the MBC indication], subject to Genentech's conduct of a new confirmatory study of Avastin with paclitaxel" (Letter from Michael Labson to the Presiding Officer, April 8, 2011, page 1). CDER has stated the issue, "Whether CDER has appropriately exercised its authority by proposing to withdraw approval of the MBC indication, rather than allowing the indication to remain on the label while the sponsor designs and conducts additional studies intended to verify the drug's clinical benefit" (CDER's Statement of Questions Presented, page 3). Ultimately, while stated differently, the parties seem to agree that there is an issue of the propriety of CDER's proposed withdrawal of this indication now as opposed to the alternative of continuing the approval of the breast cancer indication while Genentech performs new clinical studies of Avastin with paclitaxel to verify the clinical benefit of the MBC indication. This statement of the issue raises the question of why, to confirm an indication for combination use with paclitaxel, Genentech proposed, and CDER agreed, that Genentech could rely on studies of Avastin in combination with chemotherapeutic agents other than paclitaxel. It appears that the explanation is that these studies were already ongoing at the time of the initial approval and both CDER and Genentech believed, at that time, that the results of these studies could provide evidence to verify the claim that Avastin, combined with paclitaxel, would have the effect indicated in the approved labeling.

FDA is addressing the issue of whether to maintain the accelerated approval while additional studies are conducted as the third issue for this hearing as follows:

*Issue 3.* If the Commissioner agrees with the grounds for withdrawal set out in issue 1, issue 2.A, or issue 2.B, should FDA nevertheless continue the approval of the breast cancer indication while the sponsor designs and conducts additional studies intended to verify the drug's clinical benefit?

While the parties would state the issues differently, the three issues stated in this notice will be those upon which the Commissioner expects to decide this matter. If Genentech prevails on issues 1, 2.A, and 2.B, the approval will be continued. If CDER prevails on issue 1, 2.A, or 2.B, the question of withdrawal will depend on issue 3.

In addition to the issues 1, 2.A, 2.B, and 3, Genentech has proposed to raise issues concerning the consistency of CDER's position here with CDER's

decisions with respect to other products for the treatment of MBC or of other products approved under the accelerated approval program. Issues with respect to FDA action on other products are not relevant to this proceeding. Each decision to withdraw or not to withdraw the approval of a product must be made on its own merits. If the decision with respect to another product is in error, that would not justify continuing that error with respect to the MBC indication for Avastin. Moreover, as a practical matter, it would not be possible to evaluate the different circumstances associated with decisions with respect to other products in the context of this or any hearing. FDA has consistently rejected attempts to bring evidence with respect to decisions on other products into hearings on approval or withdrawal of approval of products and will not deviate from that position here.

#### *B. Process*

As further specified previously in this document, the hearing will be held in the Agency's White Oak Conference Center on June 28 and 29, 2011. Although no statute or regulation requires that separation of functions be applied to this proceeding, the Agency is observing separation of functions as a matter of policy in this matter. As the Center responsible for the proposed action, CDER, like Genentech, will be a party to the hearing and will be responsible for presenting its position at the hearing in accordance with § 601.43 and part 15.

In accordance with § 601.43(e)(2), no person other than the Presiding Officer, the three designated representatives for each party, and the members of the advisory committee may question witnesses present at the hearing.

Because this is a public hearing, it is subject to our regulations concerning the policy and procedures for electronic media coverage of public agency administrative proceedings (§§ 10.200 through 10.206 (21 CFR 10.200 through 10.206)). These procedures are primarily intended to expedite media access to our public proceedings. Representatives of the electronic media may be permitted, subject to certain limitations, to videotape, film, or otherwise record our public administrative proceedings, including the testimony of witnesses in the proceedings. Accordingly, the parties and nonparty participants to this hearing, and all other interested persons, are directed to §§ 10.200 through 10.206, for a more complete explanation of those regulations' effect on this hearing.

### III. Transcripts

Please be advised that, as soon as a transcript is available, it will be accessible at <http://www.regulations.gov>. It may be viewed at the Division of Dockets Management (see *Registration and Requests to Make Oral Presentation*). A transcript will also be available in either hardcopy or on CD-ROM, after submission of a Freedom of Information request. Written requests are to be sent to the Division of Freedom of Information (HFI-35), Office of Management Programs, Food and Drug Administration, 5600 Fishers Lane, Rm. 6-30, Rockville, MD 20857.

Dated: May 6, 2011.

**Leslie Kux,**

*Acting Assistant Commissioner for Policy.*

[FR Doc. 2011-11539 Filed 5-6-11; 4:15 pm]

**BILLING CODE 4160-01-P**

## DEPARTMENT OF HEALTH AND HUMAN SERVICES

### National Institutes of Health

#### Laboratory Animal Welfare: Proposed Adoption and Implementation of the Eighth Edition of the Guide for the Care and Use of Laboratory Animals

**AGENCY:** National Institutes of Health, HHS.

**ACTION:** Notice of Additional Extension of Comment Period.

**SUMMARY:** NIH is further extending the period for public comments on (1) NIH's adoption of the eighth edition of the *Guide for the Care and Use of Laboratory Animals (Guide)* as a basis for evaluation of institutional programs receiving or proposing to receive Public Health Service (PHS) support for activities involving animals; and (2) if NIH decides to adopt the eighth edition of the *Guide*, NIH's proposed implementation plan, which would require that institutions complete at least one semiannual program and facility evaluation using the eighth edition of the *Guide* as the basis for evaluation by March 31, 2012. NIH will consider comments on (1) The adoption of the *Guide* and (2) the implementation plan. The notice on the proposed adoption and implementation plan for the eighth edition of the *Guide* was published in the **Federal Register** on February 24, 2011 (76 FR 10379). The comment period is extended by an additional 30 days and thus will end on May 24, 2011. Additionally, character limits on the comment form fields have been removed.