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This section of the FEDERAL REGISTER contains notices to the public of the proposed issuance of rules and regulations. The purpose of these notices is to give interested persons an opportunity to participate in the rule making prior to the adoption of the final rules.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 317

[Docket No. FDA–2012–N–1037]

RIN 0910–AG92

Establishing a List of Qualifying Pathogens Under the Food and Drug Administration Safety and Innovation Act

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA or Agency) is proposing a regulation to establish a list of ''qualifying pathogens'' that have the potential to pose a serious threat to public health. The proposed rule would implement a provision of the Generating Antibiotic Incentives Now (GAIN) title of the Food and Drug Administration Safety and Innovation Act (FDASIA). GAIN is intended to encourage development of new antibacterial and antifungal drugs for the treatment of serious or life-threatening infections, and provides incentives such as eligibility for designation as a fast-track product and an additional 5 years of exclusivity to be added to certain exclusivity periods. FDA is proposing that the following pathogens comprise the list of ''qualifying pathogens:'' *Acinetobacter* species, *Aspergillus* species, *Burkholderia cepacia* complex, *Campylobacter* species, *Candida* species, *Clostridium difficile, Enterobacteriaceae* (e.g., *Klebsiella pneumoniae*), *Enterococcus* species, *Mycobacterium tuberculosis* complex, *Neisseria gonorrhoeae, N. meningitidis,* Non-tuberculous mycobacteria species, *Pseudomonas* species, *Staphylococcus aureus, Streptococcus agalactiae, S. pneumoniae, S. pyogenes,* and *Vibrio cholerae.* The preamble to the proposed rule describes the factors we considered and the methodology we used to develop this list of qualifying pathogens.

DATES: Submit comments by August 12, 2013.

ADDRESSES: You may submit comments, identified by Docket No. FDA–2012–N–1037 and/or Regulatory Information Number (RIN) 0910–AG92, by any of the following methods:

Electronic Submissions

Submit electronic comments in the following way:

- *Federal eRulemaking Portal: http://www.regulations.gov.* Follow the instructions for submitting comments.

Written Submissions

Submit written submissions in the following ways:

- *Mail/Hand delivery/Courier (for paper or CD–ROM submissions):* Division of Dockets Management (HFA–305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.

Instructions: All submissions received must include the Agency name, Docket No. FDA–2012–N–1037 and RIN 0910–AG92 for this rulemaking. All comments received may be posted without change to *http://www.regulations.gov,* including any personal information provided. For additional information on submitting comments, see the ''Comments'' heading of the **SUPPLEMENTARY INFORMATION** section of this document.

Docket: For access to the docket to read background documents or comments received, go to *http://www.regulations.gov* and insert the docket number(s), found in brackets in the heading of this document, into the ''Search'' box and follow the prompts and/or go to the Division of Dockets Management, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT: Kristiana Brugger, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave. Bldg. 51, Rm. 6262, Silver Spring, MD 20993–0002, 301–796–3601.

SUPPLEMENTARY INFORMATION:

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I. Executive Summary

Purpose of the Regulatory Action

Title VIII of FDASIA (Pub. L. 112–144), the GAIN title, is intended to encourage development of new antibacterial and antifungal drugs for the treatment of serious or life-threatening infections. Among other things, it requires that the Secretary of the Department of Health and Human Services (and thus FDA, by delegation): (1) Establish and maintain a list of ''qualifying pathogens'' that have ''the potential to pose a serious threat to public health'' and (2) make public the methodology for developing the list (see section 505E(f) of the Federal Food, Drug, and Cosmetic Act (the FD&C Act), as amended) (21 U.S.C. 355E(f)). In establishing and maintaining the list of ''qualifying pathogens,'' FDA must consider: The impact on the public health due to drug-resistant organisms in humans; the rate of growth of drug-resistant organisms in humans; the increase in resistance rates in humans;

and the morbidity and mortality in humans. FDA also is required to consult with infectious disease and antibiotic resistance experts, including those in the medical and clinical research communities, along with the Centers for Disease Control and Prevention (CDC). FDA is issuing this proposed rule to fulfill these requirements.

Summary of the Major Provisions of the Regulatory Action

After holding a public meeting and consulting with CDC and the National Institutes of Health (NIH), and considering the factors specified in section 505E(f)(2)(B)(i) of the FD&C Act, as amended, FDA is proposing that the following pathogens comprise the list of ''qualifying pathogens:'' *Acinetobacter* species, *Aspergillus* species, *Burkholderia cepacia* complex, *Campylobacter* species, *Candida* species, *Clostridium difficile, Enterobacteriaceae* (e.g., *Klebsiella pneumoniae*), *Enterococcus* species, *Mycobacterium tuberculosis* complex, *Neisseria gonorrhoeae, N. meningitidis,* Non-tuberculous mycobacteria species, *Pseudomonas* species, *Staphylococcus aureus, Streptococcus agalactiae, S. pneumoniae, S. pyogenes,* and *Vibrio cholerae.* The preamble to the proposed rule describes the factors FDA considered and the methodology FDA used to develop this list of qualifying pathogens.

Costs and Benefits

The Agency has determined that this proposed rule is not a significant regulatory action as defined by Executive Order 12866.

II. Background

Title VIII of FDASIA (Pub. L. 112–144), entitled Generating Antibiotic Incentives Now, amended the FD&C Act to add section 505E (21 U.S.C. 355E), among other things. This new section of the FD&C Act is intended to encourage development of treatments for serious or life-threatening infections caused by bacteria or fungi. For certain drugs that are designated as ''qualified infectious disease products'' (QIDPs) under new section 505E(d) of the FD&C Act, new section 505E(a) provides an additional 5 years of exclusivity to be added to the exclusivity periods provided by sections 505(c)(3)(E)(ii) to (c)(3)(E)(iv) (21 U.S.C. 355(c)(3)(E)(ii) to (c)(3)(E)(iv)), 505(j)(5)(F)(ii) to (j)(5)(F)(iv) (21 U.S.C. 355(j)(5)(F)(ii) to (j)(5)(F)(iv)), and 527 (21 U.S.C. 360cc) of the FD&C Act. In addition, an application for a drug designated as a QIDP is eligible for priority review and designation as a fast track product (sections 524A and 506(a)(1) of the FD&C Act, respectively).

The term ''qualified infectious disease product'' or ''QIDP'' refers to an antibacterial or antifungal human drug that is intended to treat serious or life-threatening infections (section 505E(g) of the FD&C Act). It includes treatments for diseases caused by antibacterial- or antifungal-resistant pathogens (including new or emerging pathogens), or diseases caused by ''qualifying pathogens.''

The GAIN title of FDASIA requires that the Secretary of the Department of Health and Human Services (and thus FDA, by designation) establish and maintain a list of such ''qualifying pathogens,'' and make public the methodology for the developing the list. According to the statute, the term 'qualifying pathogen' means a pathogen identified and listed by the Secretary * * * that has the potential to pose a serious threat to public health, such as[:] (A) resistant gram positive pathogens, including methicillin-resistant *Staphylococcus aureus,* vancomycin-resistant *Staphylococcus aureus,* and vancomycin-resistant *[E]nterococcus;* (B) multi-drug resistant gram[-]negative bacteria, including *Acinetobacter, Klebsiella, Pseudomonas,* and *E. coli* species; (C) multi-drug resistant tuberculosis; and (D) *Clostridium difficile* (section 505E(f)(1) of the FD&C Act, as amended by FDASIA). FDA is required under the law to consider four factors in establishing and maintaining the list of qualifying pathogens:

- The impact on the public health due to drug-resistant organisms in humans;
- The rate of growth of drug-resistant organisms in humans;
- The increase in resistance rates in humans; and
- The morbidity and mortality in humans (section 505E(f)(2)(B)(i), as amended by FDASIA).

Furthermore, in determining which pathogens should be listed, FDA is required to consult with infectious disease and antibiotic resistance experts, including those in the medical and clinical research communities, along with CDC (section 505E(f)(2)(B)(ii) of the FD&C Act, as amended by FDASIA). As discussed in the paragraphs that follow, FDA has met this requirement by convening a public hearing, and opening an associated public docket, to solicit input regarding the list of qualifying pathogens, as well as by consulting with infectious disease and antibiotic resistance experts at CDC and NIH during the development of this proposed rule.

Significantly, the statutory standard for inclusion on FDA's list of qualifying pathogens is different from the statutory standard for QIDP designation. QIDP designation, by definition, requires that the drug in question be an ''antibacterial or antifungal drug for human use intended to treat serious or life-threatening infections'' (section 505E(g) of the FD&C Act, as amended by FDASIA). ''Qualifying pathogens'' are defined according to a different statutory standard; the term ''means a pathogen identified and listed by the Secretary . . . that has the *potential* to pose a serious threat to public health'' (section 505E(f) of the FD&C Act, as amended by FDASIA) (emphasis added). That is, a drug intended to treat a serious or life-threatening bacterial or fungal infection caused by a pathogen that is not included on the list of ''qualifying pathogens'' may be eligible for designation as a QIDP, while a drug that is intended to treat an infection caused by a pathogen on the list may not always be eligible for QIDP designation.

FDA intends the list of qualifying pathogens to reflect the pathogens that, as determined by the Agency, after consulting with other experts and considering the factors set forth in FDASIA (see section 505E(f)(2)(B)(i) of the FD&C Act, as amended by FDASIA), have the ''potential to pose a serious threat to public health'' (section 505E(f)(1) of the FD&C Act, as amended by FDASIA). FDA does not intend for this list to be used for other purposes, such as the following: (1) Allocation of research funding for bacterial or fungal pathogens; (2) setting of priorities in research in a particular area pertaining to bacterial or fungal pathogens; or (3) direction of epidemiological resources to a particular area of research on bacterial or fungal pathogens. Furthermore, as section 505E of the FD&C Act makes clear, the list of qualifying pathogens includes only bacteria or fungi that have the potential to pose a serious threat to public health. Viral pathogens or parasites, therefore, were not considered for inclusion and are not included as part of this list.

III. Consultation With Infectious Disease and Antibiotic Resistance Experts

GAIN requires FDA to consult with infectious disease and antibiotic resistance experts, including those in the medical and clinical research communities, along with the CDC, in determining which pathogens should be included on the list of ''qualifying pathogens'' (section 505E(f)(2)(B)(ii) of the FD&C Act, as amended by FDASIA).

In order to fulfill this statutory obligation, on December 18, 2012, FDA convened a public hearing, at which the Agency solicited input regarding the following topics: (1) How FDA should interpret and apply the four factors FDASIA requires FDA to ''consider'' in establishing and maintaining the list of qualifying pathogens, (2) whether there are any other factors FDA should consider when establishing and maintaining the list of qualifying pathogens, and (3) which specific pathogens FDA should list as qualifying pathogens. The transcript of this hearing, as well as comments submitted to the hearing docket, are available at *www.regulations.gov,* docket number FDA–2012–N–1037. FDA has considered carefully the input presented at this hearing, as well as the comments submitted to the docket, in creating this proposed list of qualifying pathogens.[1] In addition, FDA consulted with experts in infectious disease and antibiotic resistance at CDC and NIH during the development of this proposed rule.

IV. Factors Considered and Methodology Used for Establishing a List of Qualifying Pathogens

As stated previously, section 505E(f)(2)(B)(i) of the FD&C Act (as amended by FDASIA) requires FDA to consider the following factors in establishing and maintaining the list of qualifying pathogens:

- The impact on the public health due to drug-resistant organisms in humans;
- The rate of growth of drug-resistant organisms in humans;
- The increase in resistance rates in humans; and
- The morbidity and mortality in humans.

The Agency recognizes it is important to take a long-term view of the drug resistance problem. For some pathogens, particularly those for which increased resistance is newly emerging, FDA recognizes that there may be gaps in the available data or evidence pertaining to one or more of the four factors described in section 505E(f)(2)(B)(i) of the FD&C Act. Thus, consistent with GAIN's purpose of encouraging the development of treatments for serious or life-threatening infections caused by bacteria or fungi, the Agency intends to consider the totality of available evidence for a particular pathogen to determine whether that pathogen should be included on the list of qualifying pathogens. Therefore, if, after considering the four factors identified in section 505E(f)(2)(B)(i) of the FD&C Act, FDA determines that the totality of available evidence demonstrates that a pathogen ''has the potential to pose a serious threat to public health,'' the Agency may designate the pathogen in question as a ''qualifying pathogen.'' More detailed explanations of each factor identified in section 505E(f)(2)(B)(i) are set forth in the paragraphs that follow.

A. The Impact on the Public Health Due to Drug-Resistant Organisms in Humans

This first factor that section 505E(f)(2)(B)(i) requires FDA to consider is also the broadest. Many factors associated with infectious diseases affect public health directly, such as a pathogen's ease of transmission, the length and severity of the illness it causes, the risk of mortality associated with its infection, and the number of approved products available to treat illnesses it causes. Additionally, although the Agency did not consider financial costs in its analyses for this proposed list of qualifying pathogens, we note that the published literature supports the conclusion that antimicrobial-resistant infections are associated with higher healthcare costs (see, e.g., Refs. 1 and 2; Ref. 3 at pp. 807, 810, 812).

In considering a proposed pathogen's impact on the public health due to drug-resistant organisms in humans, FDA will assess such evidence as: (1) The transmissibility of the pathogen and (2) the availability of effective therapies for treatment of infections caused by the pathogen, including the feasibility of treatment administration and associated adverse effects. However, FDA may also assess other public health-related evidence, including evidence that may indicate a highly prevalent pathogen's ''potential to pose a serious threat to public health'' due to the development of drug-resistance in that pathogen, even if most documented infections are currently drug-susceptible.

B. The Rate of Growth of Drug-Resistant Organisms in Humans and the Increase in Resistance Rates in Humans

The second and third factors that FDA must consider overlap substantially with one another, and for the most part are assessed using the same trends and information. Therefore, the Agency will analyze these factors together.

In considering these factors with respect to a proposed pathogen, FDA will assess such evidence as: (1) The proportion of patients whose illness is caused by a drug-resistant isolate of a pathogen (compared with those whose illness is caused by more widely drug-susceptible pathogens); (2) number of resistant clinical isolates of a particular pathogen (e.g., the known incidence or prevalence of infection with a particular resistant pathogen); and (3) the ease and frequency with which a proposed pathogen can transfer and receive resistance-conferring elements (e.g., plasmids encoding relevant enzymes, etc.). Given the temporal limitations on infectious disease data, FDA also will consider evidence that a given pathogen currently has a strong potential for a meaningful increase in resistance rates. Evidence of the potential for increased resistance may include, for example, projected (rather than observed) rates of drug resistance for a given pathogen, and current and projected geographic distribution of a drug-resistant pathogen. Furthermore, in acknowledgement of the growing problem of drug resistance, FDA may also assess other available evidence demonstrating either existing or potential increases in drug resistance rates.

C. The Morbidity and Mortality in Humans

Patients infected with drug-resistant pathogens are inherently more challenging to treat than those infected with drug-susceptible pathogens. For example, in some cases, a patient infected with a drug-resistant pathogen may have a delay in the initiation of effective drug therapy that can result in poor outcomes for such patients. Consequently, in determining whether a pathogen should be included in the list, FDA will consider the rates of mortality and morbidity (the latter as measured by, e.g., duration of illness, severity of illness, and risk and extent of sequelae from infections caused by the pathogen, and risk associated with existing treatments for such infections) associated with infection by that pathogen generally—and particularly by drug-resistant strains of that pathogen.

Setting quantitative thresholds for inclusion on the list based on any pre-specified endpoint would be inconsistent with FDA's approach of considering a totality of the evidence related to a given pathogen, as well as infeasible given the variety of pathogens under consideration. Instead, in considering whether this factor weighs in favor of including a given pathogen, the Agency will look for evidence of a meaningful increase in morbidity and mortality rates when infection with a drug-resistant strain of a pathogen is compared to infection with a more drug-

[1] The public hearing and this proposed rule share docket numbers because they are part of the same rulemaking process. Accordingly, the documents from the public hearing phase of Docket No. FDA–2012–N–1037 are included in the docket for this rulemaking.

susceptible strain of that pathogen. The Agency may also assess other evidence, such as overall morbidity and mortality rates for infection with either resistant or susceptible strains of a pathogen to determine whether that pathogen has the potential to pose a serious threat to public health, in particular if drug-resistant isolates of the pathogen were to become more prevalent in the future.

V. Proposed Pathogens for Inclusion in the List

FDA is proposing to include the following pathogens in its list of qualifying pathogens based on the data described in the paragraphs that follow. FDA expects that the inclusion of any additional pathogens in the list would be supported by similar data.

A. Acinetobacter Species

Members of the genus *Acinetobacter* are gram-negative bacteria that can cause hospital-acquired infections such as pneumonia, bacteremia (i.e., bloodstream infections), meningitis, genitourinary infections, or soft tissue infections (e.g., cellulitis) (Ref. 4 at pp. 2881–2883 (internal citation omitted)). A total of 1,490 healthcare-associated infections with *Acinetobacter* species, the majority of which were resistant to at least one class of antibacterial drugs, were reported to CDC's National Healthcare Safety Network (NHSN) in 2009–2010 (Ref. 132, Table 7). Thus, *Acinetobacter* resistance is a well-recognized and growing problem (see generally, e.g., Ref. 5), and most hospital-acquired *A. baumannii* are now resistant to multiple classes of antibacterial agents (Ref. 4 at p. 2884 (internal citation omitted)). Indeed, in recognition of this problem, in 2008, the Infectious Diseases Society of America (IDSA) designated *Acinetobacter* species to be among six highly problematic drug-resistant organisms identified as the so-called ''ESKAPE'' pathogens, which ''currently cause the majority of U.S. hospital infections and effectively 'escape' the effects of antibacterial drugs.'' [2] (Refs. 5 and 6). *Acinetobacter* species can survive for prolonged periods in the environment and on the hands of healthcare workers, and as such are well-recognized as transmissible nosocomial pathogens (see, e.g., Ref. 7). Several independent resistance mechanisms, such as those mediated by cephalosporinases, beta-lactamases, or carbapenemases, have been identified in *Acinetobacter* species, and some resistance mechanisms (e.g., genes encoding resistance-mediating enzymes) can be readily transferred from one bacteria to another on highly ambulatory genetic cassettes (Ref. 9). In addition, the pool of available effective treatments for *Acinetobacter* infections is shrinking (see, e.g., Ref. 5 at p. 7; Ref. 6).

Patients who acquire a drug-resistant *Acinetobacter* bloodstream infection appear more likely than those with drug-susceptible infections to suffer deleterious effects from the illness. For example, in a study of patients with *A. baumannii* bloodstream infections in European intensive care units (ICUs), 74 percent of *A. baumannii* bloodstream infections were resistant to a commonly used antibacterial drug (Ref. 10 at p. 33, Table 3).[3] Patients with resistant *A. baumannii* bloodstream infections became infected sooner after admission than patients with drug-susceptible *A. baumannii* (9 days vs. 19 days) (Ref. 10 at p. 33, Table 3). For those who survived, patients infected with resistant bacteria remained in the hospital longer than those infected with susceptible bacteria (20 days vs. 9 days), and, for those who died,[4] patients infected with resistant bacteria died sooner after infection than those with susceptible bacteria (5 days vs. 16 days) (Ref. 10 at p. 33, Table 3). In addition, ''recent studies of patients in the [ICU] who had [bloodstream infection] and burn infection due to [drug]-resistant *Acinetobacter* species demonstrate an increased mortality (crude mortality, 26 to 68 percent), as well as increased morbidity and length of stay in the [ICU]'' (Ref. 5 at p. 7). Similar trends have been seen for *A. baumannii* pneumonia in terms of: Prevalence of drug-resistant infection; time from admission to infection; and time from infection to death (Ref. 10).[5] In one study of Pakistani newborns with infections caused by *Acinetobacter* species, 57 of 122 *Acinetobacter*-positive cultures (from 78 newborns) showed infection in the bloodstream (Ref. 133). Approximately 71 percent of all *Acinetobacter* infections in the study were susceptible to only one antibacterial drug (polymyxin), and were labeled as a ''pan-resistant'' (i.e., resistant to many drugs) *Acinetobacter;* 47 percent of the newborns in the study with *Acinetobacter* infections died (Ref. 133).

For the reasons described previously, FDA believes that *Acinetobacter* species have the potential to pose a serious threat to the public health, particularly for hospitalized patients and, FDA is proposing to include *Acinetobacter* species in its list of qualifying pathogens.

B. Aspergillus Species

Members of the *Aspergillus* genus are fungi (specifically, hyaline molds) that have potential to cause serious infections, typically in immunocompromised people. *Aspergillus* can cause invasive infections of the lungs, skin, sinuses, bone, or brain, or be disseminated throughout the body. It frequently colonizes airway passages, creating the potential for invasive disease among patients who become immunocompromised, such as patients who receive lung transplantation (Ref. 11). In one center, for example, *Aspergillus* infection (i.e., colonization or evidence of invasive disease) was reported in approximately 30 percent of patients who received lung transplantation (Ref. 11). These fungi also may cause an allergic reaction, which may result in allergic bronchopulmonary aspergillosis, particularly in those with cystic fibrosis (CF) (Ref. 4 at pp. 3241, 3244–3249).

Invasive aspergillosis often responds poorly to antifungal therapy, even when *Aspergillus* infections are susceptible to antifungal drugs (Ref. 4 at p. 3250). Therefore, the existence throughout the world of azole-resistant *A. fumigatus* (i.e., *A. fumigatus* isolates resistant to the class of drugs comprising several different antifungal drugs in the family of ''azole antifungal drugs''), and reports that azole resistant *A. fumigatus* may be spreading in the environment (see Ref. 12 at pp. 1635–1636) is of great concern—as are the reports of multiple-drug resistant *A. fumigatus* in Europe

[2] The ''ESKAPE'' pathogens are: *Enterococcus faecium, S. aureus, Klebsiella pneumoniae, A. baumanni, Pseudomonas aeruginosa,* and *Enterobacter* species (Ref. 6).

[3] All figures represent data for those strains of *A. baumannii* whose resistance status was known, which was approximately 29 percent of all patients with *A. baumannii* bloodstream infections (Ref. 10). Numbers indicate median values (id.).

[4] The point estimate of the case fatality rate for *A. baumannii* bloodstream infections among patients in which the results of in vitro antibacterial susceptibility testing were not available for most isolates, was very high at 48 percent (68/142). The point estimate of the case fatality rate was slightly lower for known resistant infections (13/30 or 43 percent), compared to known susceptible infections (6/11 or 55 percent) (Ref. 10 at pp. 33–34). The small denominator of patients with known susceptible *A. baumannii* bloodstream infections makes it difficult to draw conclusions about a difference in mortality rates based on the in vitro susceptibility profiles; therefore any *A. baumannii* bloodstream infection, the majority of which appear to be resistant to many antibacterial drugs, is associated with a high mortality rate.

[5] For *A. baumannii* pneumonia, results of in vitro susceptibility was known for only 34 percent of patients (Ref. 10).

(Refs. 12 and 13). The predominant resistance mechanism in *A. fumigatus* is thought to be a chromosomally encoded mutation in the target enzyme, although alternative resistance mechanisms have been observed (see, e.g., Ref. 13). In some cases antifungal drugs are recommended as chemical prophylaxis to prevent invasive infections in high-risk patients (Ref. 4 at p. 3253), including some asthmatics (see Ref. 13). However, the use of prophylactic antifungal drugs creates selective pressure on these organisms, thus increasing the risk of drug-resistant *Aspergillus* colonization and infection. Moreover, European studies have found that many patients who had not received antifungal therapy nevertheless were colonized with resistant strains of *A. fumigatus* (Ref. 13 (internal citations omitted)).

Many patients with *Aspergillus* infections are vulnerable already, due to concomitant conditions such as cystic fibrosis or some level of immunodeficiency. Should *Aspergillus* resistance further diminish the already low efficacy of existing treatments and prophylaxis, patient outcomes would, similarly, be expected to worsen. For the reasons described above, FDA believes that *Aspergillus* species have the potential to pose a serious threat to the public health, and FDA is proposing to include *Aspergillus* species in its list of qualifying pathogens.

C. Burkholderia cepacia Complex

The *Burkholderia cepacia* complex (Bcc) comprises about 10 species of gram-negative bacteria (Ref. 4 at p. 2861). The *Burkholderia* genus was established relatively recently, however, and species are being identified and added to the Bcc on an ongoing basis (Ref. 4 at p. 2861). Bcc can cause pneumonia, particularly in patients with CF and patients with chronic granulomatous disease (Ref. 4 at pp. 2862, 2865 (internal citation omitted)). Bcc can also cause life-threatening bacteremia among hospitalized patients who are immunocompromised, resulting in a mortality rate of 33 percent of hematology patients with Bcc bacteremia in one academic medical center (Ref. 14). Other outbreaks of serious bacterial infections caused by Bcc have been documented due to nosocomial transmission, indicating the potential for an ease of transmissibility in the hospital setting in patients without CF (see, e.g., Ref. 15).

Bcc infections cause noteworthy levels of morbidity and mortality, particularly in patients with CF (see, e.g., Ref. 14), although outbreaks among patients without CF also have been reported (see, e.g., Ref. 16). ''Increased mortality has been observed in CF patients after colonization with Bcc,'' (Ref. 4 at p. 2865 (internal citations omitted); Ref. 17) and, in one study, survival rates for patients with CF who were infected with *B. cenocepacia* (a Bcc species) were markedly worse than rates for patients with CF who were infected with *P. aeruginosa* (not a Bcc species) (Ref. 150; see also Ref. 4 at p. 2862, Fig. 220–1 (internal citation omitted)). Because patients with CF often require repeated or chronic administration of antibacterial drugs, antibacterial drug resistance among Bcc isolates can develop through these selective pressures (see Ref. 18 (noting that an increase in antibacterial resistance was observed among patients with CF who received a chronically inhaled antibacterial drug)). In fact, a pan-resistant isolate of Bcc already has been documented in patients with CF (Ref. 19). Although there appear to be limited data on the exact incidence and prevalence of Bcc infection in the CF population, because the average life-span for patients with CF has been steadily increasing over the past few decades (Ref. 20 at p. 789, Fig. 1), it stands to reason that Bcc colonization and infection in patients with CF likely will increase. Furthermore, although data comparing outcomes of drug-resistant infections with outcomes of drug-susceptible infections also are limited, it stands to reason that decreasing susceptibility and resistance patterns in Bcc likely will be observed during the life span of a patient with CF based on selective pressures caused by appropriate use of antibacterial drugs.

For the reasons described previously, FDA believes that these pathogens have the potential to pose a serious threat to the public health—particularly for patients with CF—and FDA is proposing to include Bcc species in its list of qualifying pathogens.

D. Campylobacter Species

The *Campylobacter* genus comprises several species of gram-negative bacteria, some of which are causative agents of diarrheal and systemic diseases in humans (Ref. 4 at pp. 2793–2796). These are common infections: *Campylobacter* is estimated to cause over 1.3 million cases of enteric infection in the United States each year (Ref. 42). It is believed that most human infections are caused by consuming contaminated food (e.g., meat) or water (Ref. 4 at p. 2794), though person to person transmission of *C. jejuni* has been reported to occur through the fecal-oral route, and other routes (Ref. 4 at p. 2795). Transmissibility is readily apparent, with clinical disease that can be caused by just 500 *Campylobacter* organisms (Ref. 4 at p. 2795), so, for example, ''[e]ven one drop of juice from raw chicken meat can infect a person'' (Ref. 21).

The following indicates the potential for *Campylobacter* infections to result in enhanced morbidity and mortality, regardless of whether the bacterium is fully susceptible or is resistant to antibacterial drugs: *C. jejuni* infections have been linked to reactive arthritis in a certain subset of patients (Ref. 4 at p. 2797), *C. jejuni* infections are a major cause of Guillain-Barré syndrome (1 case per 2,000 *C. jejuni* infections, accounting for 20 to50 percent of all cases of Guillain-Barré syndrome (*id.*)), and *C. fetus* infections ''may be lethal to patients with chronic compensated diseases such as cirrhosis or diabetes mellitus or may hasten the demise of seriously compromised patients'' (Ref. 4 at p. 2799). Although many people recover from enteric *Campylobacter* infections without the need for drug treatment, a variety of antibacterial drugs, including azithromycin, erythromycin, or ciprofloxacin, may be prescribed to treat severe *Campylobacter* infections (Ref. 21; Ref. 4 at p. 2799).

Drug resistance in *Campylobacter* species, particularly resistance to fluoroquinolones, has been increasing rapidly (Ref. 4 at p. 2799 (internal citation omitted); see Ref. 22; see also Ref. 134). Indeed, in human *Campylobacter* infections, resistance has been observed to many different classes of antibacterial drugs (see, e.g., Ref. 22 (internal citations omitted); Ref. 23), and resistance mechanisms can be readily transferred from bacteria to bacteria (Ref. 22). ''Infection with *C. jejuni* strains resistant to erythromycin or fluoroquinolones is more likely to result in prolonged or invasive illness or death'' (Ref. 4 at p. 2799), and it stands to reason that drug-resistant strains of other pathogenic *Campylobacter* species are likely to be similarly problematic. One survey of *Campylobacter* isolates indicated increasing and high levels of resistance to antibacterial drugs in several classes, with some of the resistance encoded on transferable plasmids (Ref. 24). Because *Campylobacter* infections are common, any increase in resistance rates may translate quickly into a threat to the public health.

For the foregoing reasons, FDA believes that *Campylobacter* species have the potential to pose a serious threat to public health, and FDA is proposing to include bacteria from the

genus *Campylobacter* in the list of qualifying pathogens.

E. Candida Species

Candida species are fungi (specifically, yeast) that are part of the normal human flora, and thus *Candida* species can easily be transmitted and can cause invasive disease, particularly among immunocompromised patients (see, e.g., Ref. 4 at pp. 3225–3226; Ref. 25). *Candida* can infect almost any part of the body to which they are introduced (so-called invasive candidiasis), including the central nervous system, respiratory tract, urinary tract, gastro-intestinal tract, or heart (see Ref. 4 at pp. 3227–3235).

Those who are already fragile are at higher risk of invasive disease (e.g., between 5 percent and 20 percent of neonates weighing less than 2.2 pounds will develop some form of invasive candidiasis (Ref. 26)), and the risk is particularly high in those who are immunocompromised. For example, before the availability of highly-active antiretroviral therapy for the treatment of human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS), invasive candidiasis (such as esophageal candidiasis) was a common infection in this patient population, with a well-documented increase in the rates of antifungal resistance (Ref. 27). Many patients with HIV/AIDS did not respond to standard antifungal therapy and required administration of parenteral antifungal drugs, which limited therapeutic options and was directly associated with the development of resistance (Ref. 27). Today, infections caused by *Candida* species rank as the fourth most common bloodstream infection in the United States (Ref. 25). *Candida* bloodstream infections are associated with high mortality rates, with approximately 35 to 40 percent of infected patients dying of *Candida* infections in a study involving patients in one tertiary-care center (Ref. 28).

Although the problem of invasive candidiasis has diminished in the population of patients with HIV/AIDS due to advances in antiretroviral therapy, the number of patients receiving solid organ transplants, and therefore on immunosuppressive therapy, is increasing (Ref. 29). Experts are now concerned about antifungal-resistant invasive candidiasis in this patient population, echoing the concerns previously borne out in the population of patients with HIV/AIDS (see, e.g., Refs. 27 and 30). Transplant patients often take prophylactic antifungal drugs, which exert selective pressure on the *Candida* organisms and make it more likely that these patients will be colonized by, or develop infections with, drug-resistant fungi. Indeed, it has been noted that *Candida* species with antifungal resistance patterns are emerging as a common fungal infection in this population (Refs. 28 and 30).

Resistance genes in *Candida* species tend to proliferate in localized populations, though they occasionally may be transferred through mating (Ref. 31). Some reports have documented continued selective pressures of oral antifungal drugs administered as prophylaxis in certain populations, resulting in an increasing rate of infection caused by *Candida* species resistant to ''azole antifungal drugs'' (e.g., *Candida glabrata* and *Candida krusei*) (see, e.g., Refs. 32 and 33). Selective pressures from the use of oral azole antifungal drugs can shift infections from *C. albicans* to certain other *Candida* species, such as *Candida glabrata* and *Candida krusei,* which both have intrinsic resistance to azole antifungal drugs and eliminates any possibility of treatment with an oral azole antifungal drug. Thus, some patients with invasive candidiasis already have treatment options limited to only intravenously-administered antifungal drugs (Ref. 34).

For the foregoing reasons, FDA believes that *Candida* species have the potential to pose a serious threat to the public health, and FDA proposes that *Candida* species be included in the list of qualifying pathogens.

F. Clostridium difficile

C. difficile is a toxin-producing gram-positive bacterium (Ref. 35) that can cause serious, sometimes fatal, gastrointestinal disease (e.g., toxic megacolon) (see, e.g., Ref. 4 at p. 3104 (internal citation omitted)). The spores of the *C. difficile* bacteria (see Ref. 36) are difficult to eliminate from the environment, even after disinfection by hand-washing or cleansing, and individuals can acquire the pathogen via contact with either contaminated surfaces or other individuals (see, e.g., Ref. 4 at p. 3104 (internal citation omitted)). CDC estimates that the vast majority of patients with *C. difficile* infection have had recent contact with healthcare providers, either in an inpatient or outpatient setting (Ref. 37). Because spores of the bacteria are difficult to eliminate from the environment, it is not surprising that transmission of *C. difficile* infection in the hospital environment has been noted (Ref. 37).

Risk of infection with *C. difficile* increases with both a patient's age and recent antibacterial drug use (Ref. 37). Incidence of *C. difficile*-associated illness has increased significantly over the past several years. For example, ''[t]here was an 117% increase in the listing of [*C. difficile*-associated disease] on hospital discharges in the Healthcare Costs and Utilization Project Net Web site from 2000 to 2005'' (Ref. 4 at p. 3106 (internal citation omitted)), and currently, ''*C. difficile* infections are at an all-time high'' (Ref. 37). Mortality has been increasing along with infection incidence. One study showed that from 1999 to 2004 in the United States (Ref. 63) there was a 35 percent increase in mortality for which *C. difficile* infection was listed as a contributing factor. CDC has estimated a 400 percent increase in deaths between 2000 and 2007 in which *C. difficile* was a contributing factor (Ref. 37). Currently, based on a review of death certificates, about 14,000 American deaths each year list *C. difficile* infection as a contributing factor; the majority of deaths occur in patients over 65 years of age (Ref. 135).

The use of antibacterial drugs in hospitals has been identified as an important risk factor for *C. difficile* infections because *C. difficile* is naturally resistant to many commonly used antibacterial drugs. However, the prevalence of *C. difficile* infections is increasing and that has been associated with an increased prevalence of strains with new resistance to fluoroquinolones (see, e.g., Ref. 38). North American epidemiological data have shown the emergence of high levels of resistance to fluoroquinolone antibacterial drugs—and this resistance emerged quickly (see, e.g., Ref. 39). As noted by CDC, ''even a modest decrease in [drug] susceptibility might be clinically relevant'' to the epidemiology of *C. difficile* infections (Ref. 38 at p. 446). Newly acquired resistance by *C. difficile* to commonly used antibacterials, as in the case of the fluoroquinolones, facilitates the emergence of hyper-virulent strains that increase the burden of infections and deaths caused by *C. difficile* (Refs. 39 and 156).

C. difficile causes serious infections but there are a limited number of effective antibacterial drugs used to treat *C. difficile* infection, and treatment often lasts for an extended period of time (Ref. 38). Furthermore, relapse or recurrence of *C. difficile* is common, and often necessitates re-treatment with antibacterial drugs (Ref. 38). In light of these considerations, the increased prevalence of *C. difficile* infections constitutes a serious threat to the public health (Ref. 39).

Thus, FDA believes that *C. difficile* has the potential to pose a serious threat

to public health. For the reasons described previously—particularly the high prevalence of *C. difficile* infections, the fact that acquired resistance leads to increased infections and deaths via the emergence of hypervirulent strains, and the very limited treatment options—FDA is proposing to include *C. difficile* in its list of qualifying pathogens.

G. Enterobacteriaceae

The *Enterobacteriaceae* are a family of gram-negative bacteria and include species in the genera *Escherichia* (e.g., *E. coli*), *Klebsiella, Enterobacter, Shigella,* and *Salmonella* (see Ref. 4 at pp. 2815–2816). Most *Enterobacteriaceae* are toxin-secreting, and they can cause a variety of serious and life-threatening bacterial diseases (see Ref. 4 at pp. 2819–2829). For example, bloodstream infections, urinary tract infections, pneumonia, and complicated intra-abdominal infections are commonly caused by *Enterobacteriaceae,* and increasingly these infections are resistant to antibacterial drugs (see, e.g., Refs. 40 and 41). In the United States, there were 1.2 million cases of *Salmonella* infection each year (Ref. 42). In addition, the rate of hospitalization due to bloodstream infections—many of which are caused by *Enterobacteriaceae*—doubled from the years 2000 to 2008 (Ref. 43).

Antimicrobial resistance is already a problem for many genera in this family. For example, enteropathic *E. coli* strains ''are often resistant to multiple antibiotics'' (Ref. 4 at p. 2824 (internal citation omitted)) and ''resistant mutants are already present in most patients with *Enterobacter* infections before initiation of therapy'' (Ref. 4 at p. 2827). Increased resistance in *Shigella* strains has been documented in the United States (Refs. 45 and 154) and abroad (Ref. 44), as has increased resistance in *Salmonella* (Refs. 42 and 155). ''In addition, nosocomial isolates [of *Klebsiella pneumoniae*] are frequently resistant to numerous 'antibacterial drugs' as a result of the acquisition of multidrug-resistant plasmids. For example, *K. pneumoniae* is one of the most common organisms to carry plasmids encoding extended-spectrum [beta]-lactamases, and bacteremia with such strains is associated with higher rates of treatment failure and death'' (Ref. 4 at p. 2826 (internal citation omitted)).

Enterobacteriaceae resistance to beta-lactam drugs, including, for example, cephalosporins, is well-recognized (see generally, e.g., Refs. 46 and 47), and several resistant strains exist (see, e.g., Ref. 47). Extended-spectrum beta-lactamase (EBSL) enzymes may be found in several *Enterobacteriaceae* members, and these enzymes ''confer resistance against all [beta]-lactam antibiotics except carbapenems and cephamycins'' (Ref. 47 at p. 682 (internal citation omitted)).

Additionally, *Enterobacteriaceae* members can become—and, particularly in the case of *K. pneumoniae* and *E. coli,* commonly have become—resistant to carbapenems (carbapenem-resistant *Enterobacteriaceae* or CRE) (see, e.g., Ref. 48), which are beta-lactam antibiotics that ''often are the last line of defense against [g]ram-negative infections that are resistant to other antibiotics'' (Ref. 49). Recently, New Delhi metallo-beta-lactamase (NDM), a plasmid-encoded enzyme that permits bacterial resistance to broad-spectrum beta-lactam drugs, including carbapenems, has been reported in cases of *Enterobacteriaceae* infection in the United States (Refs. 50 and 51). ''CRE containing New Delhi metallo-beta-lactamase (NDM), first reported in a patient who had been hospitalized in New Delhi, India, in 2007, are of particular concern because these enzymes usually are encoded on plasmids that harbor multiple resistance determinants and are transmitted easily to other *Enterobacteriaceae* and other genera of bacteria'' (Ref. 50 (internal citations omitted); see also, e.g., Ref. 4 at p. 2820). A total of 6,470 healthcare-associated infections with *Klebsiella* species were reported to CDC's NHSN in 2009–2010; on average, approximately 11 percent were resistant to carbapenems and approximately 24 percent were non-susceptible to extended-spectrum cephalosporins. Among 9,351 *E. coli* infections reported to NHSN in 2009–2010, approximately 2 percent were resistant to carbapenems and approximately 12 percent were non-susceptible to extended-spectrum cephalosporins (Ref. 132, table 7).

Although NDM-related resistance is only one example, drug-resistance genes in *Enterobacteriaceae* ''may be present on transposons, allowing them to jump to other plasmids or chromosomes, or they may be found on integrons, which have loci downstream of strong promoters at which resistance genes may insert by site-specific recombination to be expressed at high levels'' (Ref. 4 at p. 2820; Ref. 52). It is largely for this reason that FDA is proposing to include the entire *Enterobacteriaceae* family in the list of qualifying pathogens: With each increase in resistance rates seen in one genus or species, increases in antimicrobial resistance may also occur in other pathogens in the family. It is unsurprising, then, that the proportion of drug-resistant, versus drug-susceptible, *Enterobacteriaceae* infections has increased in the past several years (see, e.g., Refs. 53 and 54). For example, a March 2013 CDC Vital Signs report documented an increase in the percentage of *Enterobacteriaceae* that were non-susceptible to carbapenems, from one to four percent in the past decade (Ref. 136).

Infections with drug-resistant strains of *Enterobacteriaceae* also result in increased rates of morbidity and mortality when compared with drug-susceptible strains of the same pathogens. In one study, the mortality rate for patients with carbapenem-resistant *K. pneumoniae* infections was 48 percent—nearly double the 26 percent mortality rate for patients with carbapenem-susceptible *K. pneumoniae* infections (Ref. 55). These differential outcomes are of particular concern, because the proportion of patients with drug-resistant versus drug-susceptible *Enterobacteriaceae* infections has increased over the past several years (see, e.g., Refs. 5 and 54).

There are a limited number of drugs with antibacterial activity for infections with multiple-drug-resistant *Enterobacteriaceae.* This means that clinicians may not always be successful in selecting an appropriate initial antibacterial drug for treatment before the availability of the results of *in vitro* antibacterial drug susceptibility testing (Ref. 55 at pp. 1104–1105 (''Our study suggests that [polymyxins, tigecycline, and aminoglycosides], alone or in combination, may not be reliably effective in the treatment of carbapenem-resistant *K. pneumoniae* infection and that newer antimicrobial agents with improved clinical activity against carbapenem-resistant *K. pneumoniae* are needed.'')). Furthermore, some last-line therapies come with different and potentially more severe adverse effects (e.g., renal toxicity) than the drugs to which many *Enterobacteriaceae* have become resistant (see, e.g., Ref. 56).

For the reasons described previously, FDA believes that *Enterobacteriaceae* has the potential to pose a serious threat to the public health, and FDA is proposing to include the *Enterobacteriaceae* family in its list of qualifying pathogens.

H. Enterococcus Species

Species in the genus *Enterococcus* are gram-positive bacteria that normally colonize the human gastrointestinal tract (Ref. 4 at p. 2643). Enterococci can cause serious disease, including bacteremia or endocarditis; *E. faecalis*

and *E. faecium* are most commonly responsible for enterococcal infections and *E. gallinarum* also has been identified as an infective agent (see Ref. 4 at pp. 2643–2647). Enterococci have been designated by the Infectious Disease Society of America as one of six highly problematic drug-resistant organisms (the so-called ''ESKAPE'' pathogens), which ''currently cause the majority of US hospital infections and effectively 'escape' the effects of antibacterial drugs.'' (Refs. 5 and 6). Although some enterococcal isolates have intrinsic resistance, other isolates have acquired resistance either from selective antibacterial pressures or from transfer of genetic resistance mechanisms from one bacterium to another, including from non-*Enterococcus* species (see, e.g., Ref. 4 at pp. 2647–2651; see also Ref. 57).

Enterococcus infections have been reported as the second most common cause of hospital-acquired infection in the United States from 1986 to 1989 (Ref. 58). Among 5,484 *E. faecium* infections associated with healthcare reported to CDC's NHSN between 2009 and 2011, approximately 80 percent were resistant to vancomycin; in this same report among 3,314 *E. faecalis* healthcare-associated infections, approximately 9 percent were resistant to vancomycin (Ref. 132, Table 7).

Enterococci infections, including infections caused by enterococci that are drug-resistant (e.g., vancomycin-resistant enterococci or VRE), are often nosocomial infections. Enterococci isolates can be resistant to multiple antibacterial drugs; in fact, *Enterococcus faecium* resistant to linezolid and resistant to vancomycin have been isolated from patients (Ref. 59), and isolates resistant to multiple antibacterial drugs were identified in a global surveillance program (see, e.g., Ref. 60). Patients with bacteremia due to VRE had an increased mortality when compared to patients who had drug-susceptible enterococcal bacteremia (Refs. 61 and 62).

In sum, for the reasons described previously—and particularly because of the increasing threat that drug-resistant enterococci pose to the public health—FDA believes that *Enterococcus* species have the potential to pose a serious threat to public health, and FDA is proposing to include *Enterococcus* species in its list of qualifying pathogens.

I. Mycobacterium tuberculosis Complex

M. tuberculosis, the bacterium that causes tuberculosis (TB), is a major global public health burden (see generally, Ref. 64). *M. tuberculosis* usually affects the lungs (pulmonary TB), but *M. tuberculosis* can affect any part of the body such as the kidney, spine, or brain (extrapulmonary TB) (Ref. 65). If TB is not properly treated, it can be fatal (see generally, Ref. 64 and Ref. 65). *M. tuberculosis* is expelled into the air when a person with TB of the lungs or throat coughs, sneezes, speaks, or sings (Ref. 65). People nearby may breathe in the organisms and become infected. *M. tuberculosis* can remain in the air for several hours, depending on the environment (Ref. 65). Factors essential for the spread of the organism are proximity and duration of contact and infectiousness of the source patient (Ref. 4 at pp. 3132, 3134). There are at least 7 species of the genus *Mycobacterium* that also cause disease similar to pulmonary tuberculosis, for example, *M. bovis, M. africanum,* and *M. microti,* among other species (Ref. 137).

Latent *M. tuberculosis* is found in one-third of the world's population (Ref. 66). In 2011, there were an estimated 8.7 million new cases and 1.4 million deaths associated with TB (Ref. 64). More than 10,000 new cases of TB were reported in 2011 in the United States (Ref. 67). Mortality figures from CDC reveal that 529 persons died in the United States from tuberculosis in 2009 (Ref. 67).

For *M. tuberculosis,* the primary mechanism of drug resistance is spontaneous chromosomal mutations, which can be amplified in the setting of inappropriate or interrupted therapy (monotherapy and combination therapy) or poor patient adherence to therapy (Ref. 68 at p. 1321). Subsequent transmission of drug-resistant *M. tuberculosis* will exacerbate the public health problem (Ref. 68). Mobile genetic elements, such as plasmids or transposons, do not appear to mediate drug resistance in *M. tuberculosis* (Ref. 68 at p. 1321). Thus, the increase in drug-resistant tuberculosis that is seen globally (see generally, Ref. 64) is a public health problem driven by inappropriate, interrupted, or poor adherence to therapy among persons being treated for TB (primary resistance), and subsequent transmission of drug-resistant *M. tuberculosis* from person to person (secondary resistance) (Ref. 68).

Isolates of *M. tuberculosis* resistant to isoniazid and rifampin, the two most important first-line antibacterial drugs used in the treatment of active TB disease, are referred to as multi-drug resistant (MDR) strains (Ref. 65). Extensively drug resistant (XDR) TB is resistant to isoniazid and rifampin, as well as two second-line drug classes (injectable agents and fluoroquinolones) (Ref. 65). Results from a multinational survey showed that 20 percent of *M. tuberculosis* isolates were MDR, and 2 percent were also XDR (Ref. 69). Resistance mechanisms are well-established for most drugs used to treat tuberculosis (Ref. 70), and drug resistant strains of tuberculosis can be transmitted from person to person, as evidenced in a 1991–1992 outbreak investigation in New York City (Ref. 71).

An epidemiological evaluation by CDC of pulmonary tuberculosis among patients in the United States found that mortality rates were higher for patients with XDR tuberculosis compared with those with MDR tuberculosis (35 percent vs. 24 percent, respectively), with the lowest mortality (10 percent) observed in patients with drug-susceptible tuberculosis (Ref. 72 at p. 2157). The authors of this report concluded that, ''[t]he emergence of XDR [tuberculosis] globally has raised concern about a return to the pre-antibiotic era in [tuberculosis] control, since XDR [tuberculosis] cases face limited therapeutic options and consequently have poor treatment outcomes and high mortality,'' (Ref. 72 at p. 2158).

For the reasons stated previously, FDA believes that *M. tuberculosis* complex has the potential to pose a serious threat to public health, and FDA is proposing to include *M. tuberculosis* complex in the list of qualifying pathogens.

J. Neisseria gonorrhoeae

N. gonorrhoeae is a nonmotile, gram-negative bacterium that can infect the mucous membrane of the urethra and cervix, as well as the rectum, oropharynx, and conjunctivae (Ref. 4 at p. 2753). The pathogen can be transmitted sexually (Ref. 73), as well as vertically from mother to newborn during delivery (Ref. 74). Gonococcal infections can cause complications, such as pelvic inflammatory disease, ectopic pregnancy, epididymitis, ophthalmitis, and endocarditis (Ref. 4 at p. 2753). Gonorrhea is the second most commonly reported notifiable disease in the United States: Over 300,000 cases of gonorrhea are reported annually (Ref. 73). However, many infections are probably undetected and unreported: CDC estimates that more than 800,000 new gonococcal infections occur annually in the United States (Ref. 75). Although the gonorrhea rate is low compared with historical trends, the rate increased during 2009–2011 (Ref. 73).

N. gonorrhoeae can acquire antibacterial drug resistance by

spontaneous chromosomal mutations arising from endogenous flora, or resistance can be acquired by transfer of genetic information from other bacteria by, for example, a plasmid-mediated resistance mechanism (Ref. 76). The Gonococcal Isolate Surveillance Project (GISP) monitors trends in antimicrobial susceptibilities of *N. gonorrhoeae* strains in the United States (Ref. 73).[6] In 2011, 30.4 percent of isolates collected in the GISP were resistant to penicillin, tetracycline, ciprofloxacin, or a combination thereof (Ref. 73).

Since 2007, the cephalosporins have been the only antibacterial drug class recommended by CDC for the first line treatment of gonorrhea (Ref. 77). On the basis of ongoing surveillance, in 2012, CDC changed its treatment guidelines to recommend dual therapy with intramuscular ceftriaxone (instead of the previously-recommended orally-administered antibacterial drug), with either azithromycin or doxycycline added not only for treatment of coinfection with *Chlamydia trachomatis,* but also to ''potentially delay emergence and spread of resistance to cephalosporins'' in *N. gonorrhoeae* (Ref. 77). This is the only remaining recommended first-line treatment regimen (Ref. 77). Reduced susceptibility of gonococcal strains to ceftriaxone has also been observed (Ref. 73). Indeed, there is a growing concern that *N. gonorrhoeae* may become resistant to all available antibacterial drugs (Ref. 78). Significantly, ''[u]nsuccessful treatment of gonorrhea with oral cephalosporins, such as cefixime, has been identified in East Asia, beginning in the early 2000s, and in Europe within the past few years. Ceftriaxone-resistant isolates have been identified in Japan (2009), France (2010), and Spain (2011)'' (Ref. 153, internal references omitted). The GISP reported that cephalosporin-resistance may now be emerging in the United States (Ref. 153).

For the reasons stated previously—particularly the increase in antibiotic resistant strains of gonorrhea together with the limited number of effective antibiotics for treatment of *N. gonorrhoeae*—FDA believes that *N. gonorrhoeae* has the potential to pose a serious threat to public health, and FDA is proposing to include *N. gonorrhoeae* on the list of qualifying pathogens.

[6] The GISP was established by the CDC in 1986 to monitor trends in antimicrobial susceptibilities of strains of *N. gonorrhoeae* in the United States to establish a rational basis for the selection of gonococcal therapies.

K. Neisseria meningitidis

N. meningitidis is an aerobic, gram-negative, fastidious diplococcus that is a leading cause of bacterial meningitis and sepsis, and can cause other serious infectious diseases, such as pneumonia, arthritis, otitis media, and epiglottitis (Ref. 79). *N. meningitidis* can be readily transmitted directly from person to person through close or prolonged contact via respiratory or throat droplets (e.g., kissing, sneezing, coughing, or living in close quarters) (Ref. 80).

Meningococcal disease is a global public health concern that remains endemic in the United States, with large epidemics of invasive disease occurring in Africa, New Zealand, and Singapore (Ref. 4 at p. 2740). Nasopharyngeal carriage of *N. meningitidis* is a precursor to disease (Ref. 4 at p. 2740), and while the majority of carriers do not develop disease, the World Health Organization estimates that, at any given time, 10 to 20 percent of the population carries *N. meningitidis* in their nasopharynx (Ref. 80). In the United States, the incidence rate is 0.15 to 0.5 per 100,000 persons (see Refs. 81 and 82). Mortality rates vary by the type of infectious disease caused by *N. meningitidis,* with a 40 percent mortality rate among patients with meningococcemia (Ref. 79), and a 13 percent mortality rate among children and adolescents with bacterial meningitis (Ref. 4 at p. 2741). Morbidity following infection with *N. meningitidis* can be substantial, including hearing loss, neurologic sequelae, and loss of limbs from amputation (Ref. 83 at p. 773).

N. meningitidis is believed to acquire resistance from the wider gene pool of other *Neisseria* species (Ref. 84 at p. 890) and through point mutations. Antibacterial drug resistance was identified as a concern in *N. meningitidis* almost 2 decades ago, with a demonstration that resistance to commonly-used antibacterial drugs were increasing in incidence, and the identification of some isolates with beta-lactamase production (i.e., the production of enzymes that cause bacteria to be resistant to beta-lactam antibacterial drugs), with the author concluding that ''this finding is of great concern,'' (Ref. 85 at p. S98). Invasive meningococcal diseases caused by isolates with reduced susceptibility to penicillin were first reported in the 1980s in the United Kingdom, Spain, and South Africa, and are now identified worldwide (Ref. 139 at p. 1016). Some countries have reported a rise in the prevalence of meningococci with reduced susceptibility to penicillin (see, e.g., Refs. 85 and 141). Case reports and studies suggest that reduced susceptibility to common antibacterial treatments used for meningococcal infection results in poorer health outcomes (Ref. 83 at p. 776). For example, a Spanish study of isolates from 1988 to 1992 found that patients with strains that had decreased drug susceptibility had higher rates of morbidity and mortality (Ref. 83 at p. 776; Ref. 149 at p. 28). Other sporadic cases of invasive *N. meningitidis* with reduced susceptibility to antibacterial drugs have been reported worldwide (see, e.g., Refs. 142 and 143). The identification of *N. meningitidis* isolates that display elevated mutability suggests an increased capacity to develop resistance, in addition to possible enhancement of transmission (see, e.g., Ref. 144).

The detection of *N. meningitidis* with reduced susceptibility or resistance to antibacterial drugs has broad and serious implications for public health, not only for treatment of patients with invasive disease, but also when considering the use of chemoprophylaxis in order to prevent cases of invasive meningococcal disease among close contacts (see, e.g., Refs. 139,142, and 143). In sum, for the reasons described previously—particularly because of the potential for higher morbidity and mortality associated with drug-resistant meningococcal infections—FDA believes that *N. meningitidis* has the potential to pose a serious threat to public health, and FDA is proposing to include *N. meningitidis* in the list of qualifying pathogens.

L. Non-Tuberculous Mycobacteria Species

Non-tuberculous *mycobacterium* (NTM) comprises several species of bacterium, including *Mycobacterium avium* complex, *M. kansasii,* and *M. abscessus* (Ref. 4 at p. 3191; Ref. 86). Other species known to cause disease include *M. fortuitum, M. chelonae, M. marinum,* and *M. ulcerans* (Ref. 4 at p. 3191). NTM are widely distributed in the environment and can be found in soil, water, plants, and animals (Ref. 4 at p. 3191). Transmission is not communicable, and it appears to occur from environmental exposure to or inhalation of the pathogen (Ref. 87 at p. 370). NTM causes many serious and life-threatening diseases, including pulmonary disease, catheter-related infections, lymphadenitis, skin and soft tissue disease, joint infections, and, in immunocompromised individuals, disseminated infection (Ref. 4 at p. 3192).

NTM infections appear to be increasing in the United States (see, e.g., Refs. 88 and 89). A recently published study of Medicare patients showed an increasing prevalence of pulmonary NTM across all regions in the United States (Ref. 89 at p. 882). The authors concluded that the annual prevalence significantly increased from 1997 to 2007 from 20 to 47 cases per 100,000 persons, respectively, or an 8.2 percent per year increase in prevalence among the Medicare population. Similarly, a population-based study in Ontario, Canada suggests an increase in the frequency of NTM infections from 9.1 per 100,000 persons in 1997 to 14.1 per 100,000 persons in 2003, resulting in an average annual increase of 8.4 percent (Ref. 90).

Antibacterial drug resistance in these organisms is ''the result of a highly complex interplay between natural resistance, inducible resistance and mutational resistance acquired during suboptimal drug exposure and selection,'' (Ref. 91 at p. 150). Treatment for NTM lung infections requires long courses of therapy, often 18 to 24 months or longer (Ref. 92 at p. 123). Because NTM is resistant to many antibacterial drugs currently available, infections caused by NTM can be difficult to treat. While there are no data from NTM isolates that indicate increasing antibacterial drug resistance, the incidence of NTM infections with intrinsic antibacterial resistance is increasing (Ref. 91). This observation raises concerns that resistant NTM may be responsible for a disproportionate share of clinical infection.

For the reasons stated previously, FDA believes that non-tuberculous mycobacteria species has the potential to pose a serious threat to public health and, FDA is proposing to include non-tuberculous mycobacteria species on the list of qualifying pathogens.

M. Pseudomonas Species

Species of the *Pseudomonas* genus are gram-negative bacteria that can cause serious infections (Ref. 4 at p. 3025). This is particularly true of *P. aeruginosa,* which ''accounted for 18.1% of hospital-acquired pneumonias and a significant percentage of urinary tract infections (16.3%), surgical site infections (9.5%), and bloodstream infections (3.4%)'' in the United States. ICUs in 2003 (Ref. 4 at p. 2837 (citing Ref. 151)). *P. aeruginosa* is ''among the top five causes of nosocomial bacteremia, and severe infection can lead to sepsis'' (Ref. 4 at p. 2847). It can grow in many environments (e.g., soil, water, and plants) (Ref. 4 at p. 2835) including moist hospital environments (e.g., showers, ventilators, mop water), and some healthy people have *P. aeruginosa* as a colonizing bacterium in their skin, throat, nose, or stool (Ref. 4 at p. 2836). *P. aeruginosa* is among the so-called ''ESKAPE'' pathogens, which ''currently cause the majority of US hospital infections and effectively 'escape' the effects of antibacterial drugs.'' (Refs. 5 and 6). *P. aeruginosa* pulmonary infection among patients with CF is associated with a more rapid decline in lung function (Ref. 18 (internal citation omitted)).

''*P. aeruginosa* now carries multiple genetically-based resistance determinants, which may act independently or in concert with others'' (Ref. 4 at p. 2856 (citing Ref. 152)). Furthermore, *P. aeruginosa* is known for its ability to ''acquire'' resistance mechanisms (see, e.g., Ref. 9). *P. aeruginosa* has been noted to develop resistance during antibacterial drug therapy even when the results of in vitro susceptibility show that the bacterium is fully susceptible when initially exposed to the antibacterial drug. (see, e.g., Ref. 93 (internal citations omitted); see also, e.g., Ref. 4 at p. 2855 (noting that in patients with *P. aeruginosa* endocarditis there is a ''likelihood of the patient's becoming resistant to therapy even if there is initially bloodstream sterilization'')). Resistant *P. aeruginosa* strains may be transmitted from person to person, or via contamination in the environment (see, e.g., Ref. 94). In a recent report from CDC's NHSN, approximately 8 percent of all healthcare-associated infections were caused by *P. aeruginosa;* among the 6,111 *P. aeruginosa* infections that were reported, approximately 25 percent were resistant to carbapenems and approximately 15 percent showed resistance in at least 3 different classes of antibacterial drugs (i.e., ''multi-drug resistant'') (Ref. 132 at Table 7).

Morbidity and mortality rates for *P. aeruginosa* infection are generally recognized as being high (see, e.g., Ref. 93 (internal citations omitted)), and infection with drug-resistant strains may have a negative effect on clinical outcomes, including an association with higher mortality (Ref. 93). Pneumonia and bloodstream infections due to drug-resistant *P. aeruginosa* have been associated with higher mortality rates in comparison to the same infections due to drug-susceptible *P. aeruginosa* (Ref. 10 at pp. 32–33, Tables 2 and 3). Although *Pseudomonas* non-*aeruginosa* infections are rare, pathogenic members of the *Pseudomonas* genus can cause serious infections and can show resistance to multiple antibacterial drugs (Ref. 95).

For the reasons described previously—including the prevalence of *Pseudomonas* infections (particularly *P. aeruginosa*), the associated high morbidity and mortality rates, the increasing antibacterial drug resistance, and the fact that the last-line antibacterial drug treatments (required to treat *Pseudomonas* infections because of its resistance to multiple classes of antibacterial drugs) often have different or more serious adverse effects—FDA believes that *Pseudomonas* has the potential to pose a serious threat to public health, and FDA is proposing to include *Pseudomonas* species in its list of qualifying pathogens.

N. Staphylococcus aureus

Staphylococcus aureus is a gram-positive bacterium that causes a variety of serious infectious diseases (Ref. 4 at p. 2543). *S. aureus* infections commonly result in skin or soft tissue infections (see, e.g., Ref. 4 at pp. 2543, 2559), and may result in more life-threatening infections (e.g., pneumonia, bloodstream), often due to infection via catheters, ventilators, or other medical devices or procedures (Ref. 96). *S. aureus* is one of the most common bacterial pathogens in hospital-acquired infections, and resistance rates for *S. aureus* have been increasing (see, e.g., Refs. 3 and 97). In addition, in the first decade of the 21st century, resistant strains of *S. aureus* (e.g., methicillin-resistant *S. aureus* or MRSA) that emerged in the community and in some hospitals are now responsible for the majority of *S. aureus* infections among outpatients (Ref. 98). In the United States in 2005, the rate of invasive MRSA infections was approximately 31.8 infections per 100,000 people (Ref. 99). *S. aureus* is also a member of the so-called ''ESKAPE'' pathogens, which ''currently cause the majority of U.S. hospital infections and effectively 'escape' the effects of antibacterial drugs.'' (Refs. 5 and 6). Reports of rapid increases in the proportion of patients hospitalized due to infections caused by MRSA were largely due to increases in skin and soft tissue infections caused by MRSA acquired in the community setting (Ref. 145). The national burden of disease due to MRSA on an outpatient basis is substantial in the United States, with an estimated 51,290 infections reported in 2010 (Ref. 146).

''*S. aureus* has developed resistance to virtually all antibiotic classes available for clinical use,'' as demonstrated by a combination of in vivo and in vitro data (Ref. 4 at p. 2558). In fact, numerous antibacterial resistance mechanisms have been documented in *S. aureus,* including the

transmission of resistance that can occur via plasmids shared between bacteria, or even transfer of resistance mechanisms from different genera of bacteria (see Ref. 100).

Patients with drug-resistant *S. aureus* infections appear to have higher mortality when compared to patients with drug-susceptible *S. aureus* infection (Ref. 10, Table 3 (showing a case fatality rate for patients with susceptible *S. aureus* bloodstream infections of 74/284 (26 percent) and a case fatality rate for patients with resistant *S. aureus* bloodstream infections of 65/171 (38 percent)). Although infections caused by vancomycin-resistant *S. aureus* (VRSA) have been very rare (see, e.g., Ref. 101), the fact that VRSA has been observed at all underscores that antibacterial drug use can exert selective pressures on *S. aureus,* effectively creating antibacterial drug resistance. When patients have infection with drug-resistant *S. aureus,* the limited options for therapy may result in concerns about the feasibility of certain therapies (e.g., some treatments involve intravenous administration, which might require hospital admission) or different adverse effect profiles that may negatively affect patients' lives (Ref. 102). It is clear, then, that drug-resistant *S. aureus* poses an increasingly serious threat to public health.

Therefore, for the reasons described previously, FDA believes that *S. aureus* has the potential to pose a serious threat to public health, and FDA is proposing to include *S. aureus* in its list of qualifying pathogens.

O. Streptococcus agalactiae

Infections caused by *S. agalactiae* (Group B *streptococcus* or GBS) are considered a major public health concern, particularly because the organism causes meningitis and sepsis in newborns due to transmission from the mother during labor and delivery (see generally, Refs. 103, 104, and 105). Maternal intrapartum antibacterial prophylaxis is recommended for pregnant women colonized with GBS, and resistance to antibacterial drugs commonly prescribed for prophylaxis is increasing (Ref. 103), thus having the potential to limit options for prophylaxis in this population. The most common diseases caused by GBS in adults are bloodstream infections, pneumonia, endocarditis, skin and soft-tissue infections, and bone and joint infections (see generally, Ref. 4 at pp. 2655–2661; Ref. 104). GBS infections can also result in other public health concerns, such as miscarriages, stillbirths, and preterm deliveries (Ref. 105).

Over the past two decades, the incidence rates of GBS have increased twofold to fourfold in nonpregnant adults, ''most of whom have underlying medical conditions or are 65 years of age or older,'' (Ref. 4 at p. 2655). The rate of invasive disease is approximately 7 per 100,000 nonpregnant adults, with the highest rate in adults aged 65 years and older at 20–25 per 100,000 persons (Ref. 106). Case-fatality rates range from 5 to 25 percent in nonpregnant adults (Ref. 4 at p. 2659).

Resistance to antibacterial drugs has emerged in GBS, with most mechanisms believed to be an inducible chromosomally-mediated resistance that can occur due to selective pressures of antibacterial drugs (Ref. 103). Recent epidemiological surveillance shows that resistance to beta-lactam antibacterial drugs, the mainstay of treatment and prevention of GBS infections, has not been identified in the United States (Ref. 107). However, there is the potential in GBS of chromosomally-mediated mechanisms conferring decreased susceptibility to beta-lactam antibacterial drugs (Ref. 108). In addition, the potential for the spread of beta-lactamases via plasmid or other genetic transfer mechanisms (see Ref. 109) to GBS will continue to be a grave concern for public health, given the pivotal role of beta-lactam antibacterial drugs for treatment and prevention of GBS infections.

CDC and researchers from other countries have described patterns of reduced susceptibility and resistance of GBS strains to common antibacterial drugs, including penicillin, macrolides, and clindamycin (see, e.g., Refs. 110 and 111). Because GBS is a common infectious disease and resistance to antibacterial drugs has been observed, it stands to reason that resistance may increase in the future.

For the foregoing reasons, FDA believes that *S. agalactiae* has the potential to pose a serious threat to public health, and FDA is proposing to include *S. agalactiae* in the list of qualifying pathogens.

P. Streptococcus pneumoniae

S. pneumoniae is a gram-positive bacterium that causes bacterial meningitis, bacteremia, respiratory tract infections including pneumonia, and otitis media (see, e.g., Refs. 112 and 113). *S. pneumoniae* can colonize the nasopharynx region, and transmission from person to person, via close contact by respiratory droplets, is thought to be common (Ref. 112). Although not all persons with *S. pneumoniae* colonization go on to develop invasive disease, colonization is a risk factor for disease.

Outbreaks of invasive pneumococcal disease are known to occur in closed populations, such as nursing homes, childcare institutions, prisons, or other institutions (Ref. 112). Invasive disease from *S. pneumoniae* is a major cause of illness and death in the United States, with an estimated 43,500 cases and 5,000 deaths in 2009 (Ref. 114). In the United States, among elderly adults hospitalized with invasive pneumonia, the mortality rate is approximately 14 percent (Ref. 115). Resistance to commonly used antibacterial drugs for treatment of *S. pneumoniae* has been observed: Surveillance studies conducted in the United States between 1994 and 2007 showed that 9 to 24 percent of pneumococci were resistant to at least 3 classes of antibiotics (Ref. 113).

High rates of antibacterial drug resistance in *S. pneumoniae* have been documented worldwide. For example, *S. pneumoniae* resistance to commonly-used antibacterial drugs has been established for several decades, with incidence of resistance to penicillin in the United States approaching 40 percent in the late 1990s (Ref. 116). In China, approximately 96 percent of all recent *S. pneumoniae* isolates were resistant to erythromycin, and multidrug resistance was prevalent in many Asian countries (Ref. 117). In certain European countries, the proportion of isolates with resistance to multiple antibacterial drugs increased from 2006 to 2009 (e.g., in Bulgaria, resistance to penicillin increased from approximately 7 percent of isolates in 2006 to approximately 37 percent of isolates in 2009) (Ref. 118 at pp. 20, 23). In the United States, some children with middle ear infection had strains of *S. pneumoniae* that were resistant to all antibacterial drugs that have an FDA-approved label for treatment of acute bacterial otitis media in children (Ref. 147). Development of resistance by *S. pneumoniae* strains to macrolide antibacterial drugs and the closely-related azolide drugs, which has been increasing in incidence, can be due to efflux-mediated mechanisms or target modifications caused by a ribosomal methylase (Ref. 148). It is speculated that increased use of macrolide antibacterial drugs may have exerted pressures in which resistance mechanisms spontaneously occurred (Ref. 148).

For the reasons described previously, including that current strains of pneumococcal disease are associated with increased resistance to commonly

used antibacterial drugs, FDA believes that *S. pneumoniae* has the potential to pose a serious threat to public health, and FDA is proposing to include *S. pneumoniae* in the list of qualifying pathogens.

Q. Streptococcus pyogenes

S. pyogenes (group A *streptococcus* or GAS) is a gram-positive bacterium that causes acute pharyngitis, in addition to other serious infectious diseases, such as necrotizing fasciitis and toxic shock syndrome (see generally, Ref. 4 at pp. 2593–2596). GAS is likely transmitted from person to person via respiratory droplets. Close personal contact, such as in schools, appears to favor spread of the organism (Ref. 4 at p. 2595).

A study published in 2003 found that approximately 1.8 million people in the United States are diagnosed with streptococcal pharyngitis annually (Refs. 119 and 120). Although streptococcal pharyngitis is typically a mild disease, in rare cases, it can result in severe post-infectious complications (see generally, Ref. 121). Though the annual incidence of invasive GAS disease is estimated to be approximately 4.3 per 100,000 persons per year, the rate of mortality associated with invasive GAS infections is high, with an estimate of 0.5 per 100,000 persons per year (Ref. 122). This means that in the United States, each year over 13,000 people are estimated to acquire an invasive GAS infection annually, and over 1,500 people are estimated to die from an invasive GAS infection (Ref. 122).

For over 80 years, GAS isolates have remained susceptible to penicillin, though reports of resistance to other antibacterial drugs have emerged in GAS, primarily by chromosomally mediated mechanisms (see generally, Refs. 123 and 124). However, recently identified genes in GAS encode for several penicillin-binding proteins, but a reason for why these genes are not expressed has yet to be determined (Ref. 123). In addition, there is an ongoing concern that transfer of antibacterial resistance to GAS by plasmid or other genetic transfer might occur at some point in the future (Ref. 109). Indeed, microbiology laboratories are encouraged to continue to perform in vitro susceptibility testing on all GAS isolates in order to monitor for the possibility of resistance (Ref. 123). Thus, given the pivotal role of the beta-lactam antibiotic penicillin in the treatment of GAS, any resistance that would occur in the future would be of great concern for public health. Antibacterial resistance in *S. pyogenes* to commonly used drugs has been reported in many countries, including the United States (Ref. 4 at p. 2599). Resistance to macrolide antibiotics and the closely related azolide group is common and poses a threat because these drugs are often used in penicillin-allergic patients (see Ref. 157). Resistance to clindamycin, a drug used for treatment of patients with necrotizing fasciitis, has also emerged (see Ref. 157).

For the reasons described previously, including the high morbidity and mortality associated with invasive infections, the frequency of less severe infections, the existing resistance to some commonly used agents and the possibility for an increase in resistant strains, GAS infections have the potential to pose a serious threat to public health and, FDA is proposing to include *S. pyogenes* in the list of qualifying pathogens.

R. Vibrio cholerae

Vibrio cholerae is a gram-negative bacterium (Ref. 4 at p. 2777) that can cause cholera, an acute diarrheal illness that can lead to severe dehydration (Ref. 125). Although cholera is found mainly in developing countries with poor sanitation and unsafe water supplies, in the United States, disease may occur in travelers returning from such countries or, more rarely, in those who have eaten contaminated food (see, e.g., Refs. 125 and 126). *V. cholerae* has the potential to cause pandemics and ''the ability to remain endemic in all affected areas'' (Ref. 4 at p. 2778 (internal citation omitted)), possibly due to the fact that infected people may shed the bacteria for several months after infection (Ref. 4 at p. 2779).

Antibacterial drug resistance in cholera-causing strains of *V. cholerae* has increased between 1990 and 2000 in U.S. patients with both domestically- and internationally-acquired infections (Ref. 126), and antibacterial drug resistance in *V. cholerae* is still increasing generally (Refs. 126, 127, 128, and 129). ''Antimicrobial drug resistance in *Vibrio* [species] can develop through mutation or through acquisition of resistance genes on mobile genetic elements, such as plasmids, transposons, integrons, and integrating conjugative elements,'' or ICEs (Ref. 127). ICEs in particular ''commonly carry several antimicrobial drug resistance genes and play a major role in the spread of antimicrobial drug resistance in *V. cholerae''* (Ref. 127 at p. 2151; Ref. 130).

Cholera-causing strains of *V. cholerae* may not cause disease in all people (Ref. 131). However, an estimated 10 percent of those infected with the O1 serogroup will develop a severe enough form of the illness that they need treatment (Ref. 131). Rehydration therapy is the most critical component of cholera treatment (see, e.g., Ref. 140). Approximately 25 to 50 percent of untreated cholera cases may prove fatal (Ref. 125). Antibiotic therapy is recommended for severely ill patients. It stands to reason that the risk of mortality in particular is likely to increase for drug-resistant *V. cholerae* infections among patients with limited treatment options.

For the reasons described previously, including the epidemic potential of toxigenic *V. cholerae* strains, as well as the ease with which this pathogen may be transmitted, this bacterium has the potential to pose a serious threat to public health, and, FDA is proposing to include *V. cholerae* in the list of qualifying pathogens.

VI. Environmental Impact

The Agency has determined under 21 CFR 25.30(h) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

VII. Analysis of Economic Impact

A. Preliminary Regulatory Impact Analysis

FDA has examined the impacts of the proposed rule under Executive Order 12866, Executive Order 13563, the Regulatory Flexibility Act (5 U.S.C. 601–612), and the Unfunded Mandates Reform Act of 1995 (Pub. L. 104–4). Executive Orders 12866 and 13563 direct agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). The Agency believes that this proposed rule is not a significant regulatory action as defined by Executive Order 12866.

The Regulatory Flexibility Act requires agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities. Because the proposed rule would not impose direct costs on any entity, regardless of size, but rather would clarify certain types of pathogens for which the development of approved treatments might result in the awarding of QIDP designation and exclusivity to sponsoring firms, FDA proposes to certify that the final rule would not have

a significant economic impact on a substantial number of small entities.

Section 202(a) of the Unfunded Mandates Reform Act of 1995 requires that agencies prepare a written statement, which includes an assessment of anticipated costs and benefits, before proposing ''any rule that includes any Federal mandate that may result in the expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of $100,000,000 or more (adjusted annually for inflation) in any one year.'' The current threshold after adjustment for inflation is $139 million, using the most current (2011) Implicit Price Deflator for the Gross Domestic Product. FDA does not expect this proposed rule to result in any 1-year expenditure that would meet or exceed this amount.

B. Background

Antibacterial research and development has reportedly declined in recent years. A decrease in the number of new antibacterial products reaching the market in recent years has led to concerns that the current drug pipeline for antibacterial drugs may not be adequate to address the growing public health needs arising from the increase in antibiotic resistance. A number of reasons have been cited as barriers to robust antibacterial drug development including smaller profits for short-course administration of antibacterial drugs compared with long-term use drugs to treat chronic illnesses, challenges in conducting informative clinical trials demonstrating efficacy in treating bacterial infections, and growing pressure to develop appropriate limits on antibacterial drug use.

One mechanism that has been used to encourage the development of new drugs is exclusivity provisions which provide for a defined period during which an approved drug is protected from submission or approval of certain potential competitor applications. By securing additional guaranteed periods of exclusive marketing, during which a drug sponsor would be expected to benefit from associated higher profits, drugs that might not otherwise be developed due to unfavorable economic factors may become commercially attractive to drug developers.

In recognition of the need to stimulate investments in new antibiotic drugs, Congress enacted the GAIN title of FDASIA to create an incentive system. The primary framework for encouraging antibiotic development became effective on July 9, 2012, through a self-implementing provision that authorizes FDA to designate human antibiotic or antifungal drugs that treat ''serious or life-threatening infections'' as QIDPs. With certain limitations set forth in the statute, a sponsor of an application for an antibiotic or antifungal drug that receives a QIDP designation gains an additional 5 years of exclusivity to be added to certain exclusivity periods for that product. Drugs that receive a QIDP designation are also eligible for designation as a fast-track product and an application for such a drug is eligible for priority review.

C. Need for and Potential Effect of the Regulation

Between July 9, 2012, when the GAIN title of FDASIA went into effect, and January 31, 2013, FDA granted 11 QIDP designations. As explained previously, the statutory provision that authorizes FDA to designate certain drugs as QIDPs is self-implementing, and inclusion of a pathogen on the list of ''qualifying pathogens'' does not determine whether a drug proposed to treat an infection caused by that pathogen will be given QIDP designation. However, section 505E(f) of the FD&C Act, added by the GAIN title of FDASIA, requires that FDA establish a list of ''qualifying pathogens.'' This proposed rule is intended to satisfy that obligation, as well as the statute's directive to make public the methodology for developing such a list of ''qualifying pathogens.'' The proposed rule identifies 18 ''qualifying pathogens,'' including those provided as examples in the statute, which FDA has concluded have ''the potential to pose a serious threat to public health'' and proposes to include on the list of ''qualifying pathogens.''

As previously stated, this proposed rule would not change the criteria or process for awarding QIDP designation, or for awarding extensions of exclusivity periods. That is, the development of a treatment for an infection caused by a pathogen included in the list of ''qualifying pathogens'' is neither a necessary nor a sufficient condition for obtaining QIDP designation, and, as stated in section 505E(c) of the FD&C Act, not all applications for a QIDP are eligible for an extension of exclusivity. Relative to the baseline in which the exclusivity program under GAIN is in effect, we anticipate that the incremental effect of this rule would be negligible.

To the extent that this rule causes research and development to shift toward treatments for infections caused by pathogens on the list and away from treatments for infections caused by other pathogens, the opportunity costs of this rule would include the forgone net benefits of products that treat or prevent pathogens not included in the list, while recipients of products to treat infections caused by pathogens on the list would receive benefits in the form of reduced morbidity and premature mortality. Sponsoring firms would experience both the cost of product development and the economic benefit of an extension of exclusivity and of potentially accelerating the drug development and review process with fast-track status and priority review. If this rule induces greater interest in seeking QIDP designation than would otherwise occur, FDA would also incur additional costs of reviewing applications for newly-developed antibacterial or antifungal drug products under a more expedited schedule.

Given that the methodology for including a pathogen in the list of ''qualifying pathogens'' was developed with broad input, including input from industry stakeholders and the scientific and medical community involved in anti-infective research, we expect that the pathogens listed in this proposed rule reflect not only current thinking regarding the types of pathogens which have the potential to pose serious threat to the public health, but also current thinking regarding the types of pathogens that cause infections for which treatments might be eligible for QIDP designation. To the extent that there is overlap between drugs designated as QIDPs and drugs developed to treat serious or life-threatening infections caused by pathogens listed in this proposed rule, this proposed rule would have a minimal impact in terms of influencing the volume or composition of applications seeking QIDP designation, compared to what would otherwise occur in the absence of this rule.

VIII. Paperwork Reduction Act

FDA concludes that this proposed rule does not contain a ''collection of information'' that is subject to review by the Office of Management and Budget under the Paperwork Reduction Act of 1995 (the PRA) (44 U.S.C. 3501–3520). This proposed rule interprets some of the terms used in section 505E of the FD&C Act and proposes ''qualifying pathogen'' candidates. Inclusion of a pathogen on the list of ''qualifying pathogens'' does not confer any information collection requirement upon any party, particularly because inclusion of a pathogen on the list of ''qualifying pathogens,'' and the QIDP designation process, are distinct processes with differing standards.

The QIDP designation process will be addressed separately by the Agency at a later date. Accordingly, the Agency will analyze any collection of information or

additional PRA-related burdens associated with the QIDP designation process separately.

IX. Federalism

FDA has analyzed this proposed rule in accordance with the principles set forth in Executive Order 13132. FDA has determined that the proposed rule, if finalized, would not contain policies that would have substantial direct effects on the States, on the relationship between the National Government and the States, or on the distribution of power and responsibilities among the various levels of government. Accordingly, the Agency tentatively concludes that the proposed rule does not contain policies that have federalism implications as defined in the Executive order and, consequently, a federalism summary impact statement is not required.

X. Comments

Interested persons may submit either electronic comments regarding this document to *http://www.regulations.gov* or written comments to the Division of Dockets Management (see **ADDRESSES**). It is only necessary to send one set of 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, and will be posted to the docket at *http://www.regulations.gov*.

XI. References

The following references have been placed on display in the Division of Dockets Management (see **ADDRESSES**) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday, and are available electronically at *http://www.regulations.gov*. (FDA has verified the Web site addresses in this reference section, but we are not responsible for any subsequent changes to Web sites after this document publishes in the **Federal Register**.)

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List of Subjects in 21 CFR Part 317

Antibiotics, Communicable diseases, Drugs, Health, Health care, Immunization, Prescription drugs, Public health.

Therefore, under the Federal Food, Drug, and Cosmetic Act, and under authority delegated to the Commissioner of Food and Drugs, 21 CFR part 317 is proposed to be added to read as follows:

PART 317—QUALIFYING PATHOGENS

Sec.
317.1 [Reserved]
317.2 List of qualifying pathogens that have the potential to pose a serious threat to public health.

Authority: 21 U.S.C. 355E, 371.

§ 317.2 List of qualifying pathogens that have the potential to pose a serious threat to public health.

The term ''qualifying pathogen'' in section 505E(f) of the Federal Food, Drug, and Cosmetic Act is defined to mean any of the following:

(a) *Acinetobacter* species.
(b) *Aspergillus* species.
(c) *Burkholderia cepacia* complex.
(d) *Campylobacter* species.
(e) *Candida* species.
(f) *Clostridium difficile.*
(g) *Enterobacteriaceae.*
(h) *Enterococcus* species.
(i) *Mycobacterium tuberculosis* complex.
(j) *Neisseria gonorrhoeae.*
(k) *Neisseria meningitidis.*
(l) Non-tuberculous mycobacteria species.
(m) *Pseudomonas* species.
(n) *Staphylococcus aureus.*
(o) *Streptococcus agalactiae.*
(p) *Streptococcus pneumoniae.*
(q) *Streptococcus pyogenes.*
(r) *Vibrio cholerae.*

Dated: June 5, 2013.

Leslie Kux,

Assistant Commissioner for Policy.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 890

[Docket No. FDA–2013–N–0568]

Physical Medicine Devices; Reclassification of Stair-Climbing Wheelchairs

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed order.

SUMMARY: The Food and Drug Administration (FDA) is issuing a proposed administrative order to reclassify stair-climbing wheelchairs, a class III device, into class II (special controls) based on new information and subject to premarket notification, and to further clarify the identification.

DATES: Submit either electronic or written comments on this proposed order or on the draft guideline by September 10, 2013. See section XII for the proposed effective date of any final order that may publish based on this proposed order.

ADDRESSES: You may submit comments, identified by Docket No. FDA–2013–N–0568 by any of the following methods:

Electronic Submissions

Submit electronic comments in the following way:

• *Federal eRulemaking Portal: http://www.regulations.gov*. Follow the instructions for submitting comments.

Written Submissions

Submit written submissions in the following ways: