a Submission Agreement, Submission Information Form (SIF) or other, similar data producer-archive agreement.

(g) *Budget Plan.* The Strategic Operational Plan shall include or reference a Budget Plan that:

(1) Identifies who supports the RICE financially;

(2) Identifies how RICE priorities guide funding decisions; and

(3) Assesses funding constraints and the associated risks to the observing System that the RICE must address for the future.

§ 997.24 Gaps identification.

(a) To become certified, a RICE must identify gaps in observation coverage needs for capital improvements of Federal assets and non-Federal assets of the System, or other recommendations to assist in the development of annual and long-terms plans and transmit such information to the Interagency Ocean Observing Committee via the Program Office.

(b) The application shall:

(1) Document that the RICE's asset inventory contains up-to-date information. This could be demonstrated by a database or portal accessible for public viewing and capable of producing a regional summary of observing capacity;

(2) Provide a regional Build-out Plan that identifies the regional priorities for products and services, based on its understanding of regional needs, and a description of the integrated system (observations, modeling, data management, product development, outreach, and R&D). The RICE shall review and update the Build-out Plan at least once every five years; and

(3) Document the priority regional gaps in observation coverage needs, as determined by an analysis of the RICE asset inventory and Build-out Plan. The RICE shall review and update the analysis of priority regional gaps in observation coverage needs at least once every five years.

§ 997.25 Financial oversight.

(a) To become certified, a RICE must comply with all financial oversight requirements established by the Administrator, including requirement relating to audits.

(b) The application shall document compliance with the terms and conditions set forth in 2 CFR Part 215—Uniform Administrative Requirements for Grants and Agreements with Institutions of Higher Education, Hospitals, and Other Non-profit Organizations, Subpart C—Post Award Requirements. Subpart C prescribes standards for financial management systems, among others. (Compliance with this criterion can be demonstrated by referencing any existing grant, cooperative agreement, or contract the RICE has with NOAA.)

(c) The RICE shall document annually the RICE's operating and maintenance costs for all observing platforms and sensors, etc., owned and/or operated by the RICE. This information shall be made available to NOAA upon request.

§ 997.26 Civil liability.

(a) For purposes of determining liability arising from the dissemination and use of observation data gathered pursuant to the ICOOS Act and these regulations, any non-Federal asset or regional information coordination entity incorporated into the System by contract, lease, grant, or cooperative agreement that is participating in the System shall be considered to be part of the National Oceanic and Atmospheric Administration. Any employee of such a non-Federal asset or regional information coordination entity, while operating within the scope of his or her employment in carrying out the purposes of this subtitle, with respect to tort liability, is deemed to be an employee of the Federal Government.

(b) The ICOOS Act's grant of civil liability protection (and thus the RICE's limited status as part of NOAA) applies only to a RICE that:

(1) Is participating in the System, meaning the RICE has been certified by NOAA in accordance with the ICOOS Act and these regulations; and

(2) Has been integrated into the System by memorandum of agreement with NOAA.

(c) An ''employee'' of a regional information coordination entity is an individual who satisfies all of the following requirements:

(1) The individual is employed or contracted by a certified RICE that has been integrated into the System by memorandum of agreement with NOAA, and that is participating in the System, as defined in § 997.26(b);

(2) The individual is identified by the RICE, as required in § 997.23(d)(3) and (f)(1)(i), as one of the individuals responsible for the collection, management, or dissemination of ocean, coastal, and Great Lakes observation data; and

(3) The individual is responsive to federal government control.

(d) The protection afforded to employees of a RICE with regard to liability applies only to specific individuals employed or contracted by a RICE who meet the requirements of § 997.26(c) and who are responsible for the collection, management, or dissemination of ocean, coastal, and Great Lakes observation data. The RICE must identify to NOAA's satisfaction: The individual(s) responsible for overall system management, as applicable, the individual(s) responsible for observations system management across the region, and the individual(s) responsible for management of data operations across the region. In accepting certification, the RICE will concede to NOAA the power to ensure these individuals comply with the requirements of this rule in their daily operations and that they are responsive to NOAA through the agreement the RICE has with NOAA.

[FR Doc. 2014–13034 Filed 6–4–14; 8:45 am]

BILLING CODE 3510–JE–P

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: Final rule.

SUMMARY: The Food and Drug Administration (FDA or Agency) is issuing a regulation to establish a list of ''qualifying pathogens'' that have the potential to pose a serious threat to public health. This final rule implements 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. Based on analyses conducted both in the proposed rule and in response to comments to the proposed rule, FDA has determined that the following pathogens comprise the list of ''qualifying pathogens:'' *Acinetobacter* species, *Aspergillus* species, *Burkholderia cepacia* complex, *Campylobacter* species, *Candida* species, *Clostridium difficile,*

Coccidioides species, *Cryptococcus* species, Enterobacteriaceae (e.g., *Klebsiella pneumoniae*), *Enterococcus* species, *Helicobacter pylori, 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 described the factors the Agency considered and the methodology used to develop the list of qualifying pathogens. As described in the preamble of this final rule, FDA applied those factors and that methodology to additional pathogens suggested via comments on the proposed rule.

DATES: This rule is effective July 7, 2014.

ADDRESSES: For access to the docket to read background documents or comments received, go to *http://www.regulations.gov* and insert the docket number, 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.

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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, GAIN 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 by FDASIA) (21 U.S.C. 355f(f)). In establishing and maintaining the list of ''qualifying pathogens,'' FDA must consider the following factors: 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 (see section 505E(f)(2)(B)(i) of the FD&C Act). 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) (see section 505E(f)(2)(B)(ii) of the FD&C Act). FDA issued a proposed rule on June 12, 2013 (78 FR 35155), and, after analyzing comments to that proposed rule, is issuing this final rule in fulfillment of the statutory requirements described above.

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, FDA proposed on June 12, 2013, 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. After analyzing comments to the proposed rule, FDA has decided to retain the previously proposed methodology for developing the list of qualifying pathogens and will include the pathogens identified in the proposed rule on the list of qualifying pathogens. FDA also has applied the methodology set forth in the proposed rule to additional pathogens suggested by comments to the proposed rule. Based on these analyses, FDA also will add *Coccidioides* species, *Cryptococcus* species, and *Helicobacter pylori* to the list of qualifying pathogens. The table below describes the pathogen lists for the proposed and final rule for comparison:

Proposed rule	Final rule
Acinetobacter species	*Acinetobacter* species.
Aspergillus species	*Aspergillus* species.
Burkholderia cepacia complex	*Burkholderia cepacia* complex.
Campylobacter species	*Campylobacter* species.
Candida species	*Candida* species.
Clostridium difficile	*Clostridium difficile.*
Enterobacteriaceae	*Enterobacteriaceae.*
Enterococcus species	*Enterococcus* species.
Mycobacterium tuberculosis complex	*Mycobacterium tuberculosis* complex.
Neisseria gonorrhoeae	*Neisseria gonorrhoeae.*
Neisseria meningitidis	*Neisseria meningitidis.*
Non-tuberculous mycobacteria species	Non-tuberculous mycobacteria species.
Pseudomonas species	*Pseudomonas* species.
Staphylococcus aureus	*Staphylococcus aureus.*
Streptococcus agalactiae	*Streptococcus agalactiae.*

Proposed rule	Final rule
Streptococcus pneumoniae	*Streptococcus pneumoniae.*
Streptococcus pyogenes	*Streptococcus pyogenes.*
Vibrio cholerae	*Vibrio cholerae.*
	Coccidioides species.
	Cryptococcus species.
	Helicobacter pylori.

Costs and Benefits

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

I. Background: FDASIA Requirements

Title VIII of FDASIA (Pub. L. 112–144), entitled Generating Antibiotic Incentives Now, amended the FD&C Act to add section 505E, 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 (21 U.S.C. 356n–I and 556(a)(1)), 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). The term 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 delegation) 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). 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) of the FD&C Act).

Further, in determining which pathogens should be listed, 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). 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 (77 FR 68789, November 16, 2012). The transcript of this hearing, as well as comments submitted to the hearing docket, are available at *http://www.regulations.gov,* docket number FDA–2012–N–1037. FDA considered carefully the input presented at this hearing, as well as the comments submitted to the hearing docket, in creating the 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 both the proposed and the final rule.

II. Proposed Rule and Final Rule

On June 12, 2013, FDA published the proposed rule, ''Establishing a List of Qualifying Pathogens Under the Food and Drug Administration Safety and Innovation Act'' (78 FR 35155). In the proposed rule, the Agency set forth the factors it proposed to consider and the methodology it proposed to use in establishing the list of qualifying pathogens, as well as its interpretation of statutory language. The Agency concluded with extensive analyses of the 18 pathogens proposed for inclusion on the list of ''qualifying pathogens.'' FDA's decisions regarding the proposed rule are described in sections III.A, III.B, III.C, and IV.

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

After reviewing the comments submitted to the docket (see section IV), the Agency has decided to finalize the proposed factors for consideration and methodology for establishing the list of qualifying pathogens, and has reiterated them below for convenience.

As stated previously, section 505E(f)(2)(B)(i) of the FD&C Act 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

[1] The public hearing and this 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.

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 will identify the pathogen in question as a ''qualifying pathogen.'' More detailed explanations of each factor identified in section 505E(f)(2)(B)(i) of the FD&C Act are set forth in the paragraphs that follow.

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

This first factor that section 505E(f)(2)(B)(i) of the FD&C Act 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 also may 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.

2. 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 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) the 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 also may assess other available evidence demonstrating either existing or potential increases in drug resistance rates.

3. 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 on 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 prespecified 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-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.

B. Finalization of Statutory Interpretation

As FDA explained in the proposed rule (78 FR 35155 at 35156) and affirms in this final rule, 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). ''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) (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. After reviewing the comments to the docket on this point (see section IV.A), FDA's understanding of these statutory standards remains unchanged.

To alleviate confusion regarding this issue, FDA also clarifies that vaccine applications are ineligible for QIDP designation under the GAIN title of FDASIA. Vaccines are biological products whose applications for approval are submitted under section 351 of the Public Health Service Act (the PHS Act) (42 U.S.C. 262). QIDPs,

however, must be human drugs whose applications are submitted pursuant to section 505(b) of the FD&C Act. Thus, under the law, vaccines are ineligible for QIDP designation.

As stated in the proposed rule (78 FR 35156) and affirmed in this final rule, 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), have the ''potential to pose a serious threat to public health'' (section 505E(f)(1) of the FD&C Act). 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.

C. Finalization of Proposed Pathogens for Inclusion on the List

FDA's proposed rule concluded with an analysis of the 18 pathogens the Agency proposed to identify as qualifying pathogens. After reviewing the comments to the docket (see section IV.C), FDA is finalizing its analyses of the 18 proposed pathogens as written in the proposed rule (see 78 FR 35155 at 35158 through 35166), which are incorporated by reference herein, and is identifying all 18 proposed pathogens as ''qualifying pathogens'' in § 317.2 (21 CFR 317.2).

D. Inclusion of Additional Pathogens on the List of Qualifying Pathogens

In response to comments, FDA has added three additional pathogens (*Coccidiodes* species, *Cryptococcus* species, and *Helicobacter pylori*) to the list of qualifying pathogens (see section IV.D).

III. Comments to the Proposed Rule and FDA's Responses

After the publication of the proposed rule on June 12, 2013, 18 comments from pharmaceutical companies, lawmakers and governmental organizations, infectious disease specialists, public interest groups, and other members of the public were submitted to the docket via *http://www.regulations.gov* during the 60-day comment period. FDA has summarized and responded to these comments below. To make it easier to identify the comments and FDA's responses, the word ''Comment,'' in parentheses, appears before the comment's description, and the word ''Response,'' in parentheses, appears before the Agency's response. We have numbered each comment to help distinguish between different comments. Similar comments are grouped together under the same number, and, in some cases, different subjects discussed in the same comment are separated and designated as distinct comments for purposes of FDA's responses. The number assigned to each comment or comment topic is purely for organizational purposes and does not signify the comment's value or importance or the order in which comments were received.

A. Statutory Interpretation and Proposed Factors for Consideration

(Comment 1) One comment criticized FDA's interpretation of the statute that not all treatments for infections caused by qualifying pathogens will be eligible for QIDP designation, and that ''the development of a treatment for an infection caused by a pathogen included on the list of 'qualifying pathogens' is neither a necessary nor a sufficient condition for obtaining QIDP designation'' (78 FR 35515 at 35167). The comment first expressed concern that, because the terms ''serious'' and ''life-threatening'' are not separately defined by statute, their meanings could change in the future. The comment contrasted this alleged uncertainty with the statute's detailed definition and identification process for ''qualifying pathogens,'' asserting that the collective term ''serious or life-threatening infections'' includes infections caused by qualifying pathogens. Thus, the comment asserted, Congress intended the qualifying pathogen list to provide ''some certainty and transparency'' regarding which products may be eligible for QIDP designation.

(Response) FDA agrees with the comment that the term ''serious or life-threatening'' is not explicitly defined in the statute. Nevertheless, the Agency has been interpreting and applying these terms in the context of other programs under the Food, Drug, and Cosmetic Act intended to expedite the development of drugs and biologics to address unmet medical needs for several years. ''Serious or life-threatening'' is used in section 506 of the FD&C Act, in the context of expedited programs, including fast track designation. The term ''serious'' is further defined in a 2006 FDA guidance for industry, ''Fast Track Drug Development Program—Designation, Development, and Application Review (which will be superseded by the draft guidance for industry, ''Expedited Programs for Serious Conditions—Drugs and Biologics,'' when finalized) and in the preamble to a final rule pertaining to accelerated approval (57 FR 58942, December 11, 1992). The term ''life-threatening'' is defined in 21 CFR 312.81(a). The provisions related to QIDPs in GAIN similarly seek to incentivize the development of drugs to meet an unmet medical need and, indeed, QIDP-designated applications are eligible for both priority review and fast-track designation (see section 524A of the FD&C Act and section 506(b)(1) of the FD&C Act, as amended). The Agency intends, therefore, to interpret serious or life-threatening in a similar manner with respect to GAIN as it has in the context of these expedited programs. While guidances and even regulations may change, the Agency may not apply different definitional standards to similarly situated applicants or applications. Thus, concerns over lack of a statutory definition of ''serious or life-threatening'' are an insufficient basis for FDA to change its interpretation of the statute.

Further, it may be true that many of the qualifying pathogens listed by FDA may cause serious or life-threatening infections for which treatments might be eligible for QIDP designation. However, the comment's assertions cannot change the language that *is* in the statute, which provides different standards for QIDPs and qualifying pathogens. Qualifying pathogens are ''*pathogen[s] . . .* that ha[ve] the *potential* to pose a *serious threat to public health,''* whereas QIDPs are certain human ''*drugs . . .* intended to treat *serious or life-threatening infections''* (emphasis added). Most importantly, many pathogens with the *potential* to seriously threaten public health may cause varying levels of morbidity and mortality in a given individual depending on the site of infection, the person infected, the level of antimicrobial resistance present in the infecting pathogen, and other factors.

(Comment 2) One comment stated that only ''factors that can be addressed through new drug development'' should be used as criteria for including pathogens on the list. The comment does not specify which factors these are, but the comment's concerns stem from an assertion that new drugs contribute to antibiotic resistance due to their off-

label use, use in patients who do not need the drugs, or use in patients whose underlying infection is unidentified.

(Response) FDA agrees that good antibiotic stewardship is critical in reducing antibiotic resistance rates. However, the mandatory statutory considerations specified in section 505E(f)(2)(B)(i) of the FD&C Act are not limited to factors that can be addressed only through new drug development. FDA will make no changes to the rule based on this comment.

(Comment 3) One comment asserted that rarely used, non-''standard of care'' drugs should be considered in assessing the therapies available to treat a given pathogen. FDA understands this comment to mean that FDA should include, in its assessment of available therapies for infections by particular pathogens, drugs that may treat those infections but nevertheless are not considered ''standard of care'' therapies.

(Response) FDA considers the number of approved products available to treat infectious diseases caused by a pathogen when assessing the impact on the public health due to drug-resistant bacterial or fungal pathogens in humans. For the purposes of this list of qualifying pathogens, at this time, FDA will not consider unapproved products or off-label use of products approved for another indication. FDA will make no changes to the rule based on this comment.

(Comment 4) One comment agreed that incentives authorized by GAIN for the creation of new antibacterial and antifungal drugs should focus on drugs that treat serious or life-threatening infections.

(Response) FDA responds by confirming that QIDP designation, which is a prerequisite to the incentives authorized by GAIN, may be made for ''antibacterial or antifungal drug[s] for human use intended to treat serious or life-threatening infections'' (section 505E(g) of the FD&C Act). FDA will make no changes to the rule in response to this comment.

(Comment 5) Another comment found FDA's proposed methodology and rationale for inclusion of qualifying pathogens to be favorable, and agreed with the Agency that the statute provides different definitions for ''qualifying pathogens'' and QIDPs. The comment also asserted that having QIDP designation depend on intended indication (i.e., treatment of serious or life-threatening infections) is what reflects statutory intent, rather than having QIDP status depend on targeting specific pathogens.

(Response) FDA agrees with the points made in this comment. FDA's interpretation and application of the GAIN provision is consistent with the intent of the statute, which is to use exclusivity and other incentives to spur development of the most urgently needed treatments, i.e., those treating serious or life-threatening infections. The Agency will make no changes to the proposed rule as a result.

B. Miscellaneous Comments

(Comment 6) One comment pointed out that FDA did not provide a basis for excluding the pathogens not listed on the qualifying pathogen list. The comment also stated that FDA ''fails to mention'' how the pathogens on the qualifying pathogen list and the pathogens *not* on the qualifying pathogen list may relate to other pathogen lists (e.g., those pertaining to bioterrorism).

(Response) FDA reiterates that the focus of this rulemaking is to fulfill statutory requirements to: (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 FD&C Act). Other pathogen lists, including CDC's list of bioterrorism agents/diseases, have different purposes and standards. FDA will not, nor is it required to, make comparisons between and among the qualifying pathogen list (or the pathogens *not* appearing on the list) and ''additional lists'' of pathogens.

In responding to comments received on the proposed rule, however, the Agency will explain why it either accepted or rejected comment requests to add particular pathogens.

For the foregoing reasons, FDA will make no changes to the contents of the proposed rule based on this comment.

(Comment 7) One comment asserted that pathogens with approved ''reserve antibiotics'' should ''not automatically count as qualifying pathogens.'' FDA understands this comment to suggest that pathogens whose infections may be treated with ''reserve antibiotics'' (i.e., antibacterial drugs that are placed ''in reserve'' for those patients who have very limited options for treatment of their bacterial infections, but are not widely used to treat patients who have many antibacterial treatment options available to treat their bacterial infections) should not be on the list of qualifying pathogens.

(Response) In making its ''qualifying pathogen'' determinations, FDA does consider the therapies—including ''reserve antibiotics''—that are available and indicated to treat infections with a given pathogen. Nevertheless, the fact that some pathogens already have approved antimicrobial therapies available is not dispositive of whether a particular pathogen meets the several statutory criteria FDA must assess. Furthermore, as a general matter, subsequent new drug development following the first drug approval could address important public health issues in patients with unmet need based on one or more of the following considerations:

- Alternative drugs may be needed to treat special populations (e.g., renal impairment) or patients for whom drug interactions are a concern.
- Some patients may experience an adverse drug effect and be unable to complete the course of therapy.
- Some patients may have an allergy to certain drugs and need alternatives.
- In some circumstances, drug production issues may arise that affect supply for a drug.
- New information may become evident postmarketing that has an impact on risk/benefit for some patients.

FDA will make no changes to the rule in response to this comment.

(Comment 8) One comment stated that ''when new therapies are created and used to treat qualifying pathogens, these should be removed from the list.''

(Response) FDA interprets this comment to mean that, as soon as FDA approves a new drug to treat an infection caused by one of the qualifying pathogens, that pathogen should be removed from the list. FDA responds by noting that the availability of effective therapies for treating infections with a given pathogen is merely one consideration among many that FDA considers in determining whether a pathogen should be designated a ''qualifying pathogen.'' While important to FDA's assessment, the availability of effective therapies does not determine whether a qualifying pathogen should remain on the list. FDA will reassess the list of qualifying pathogens ''every 5 years, or more often as needed,'' according to the requirements of the statute (see 505E(f)(2)(C) of the FD&C Act), and declines to establish a single-standard trigger for removing pathogens from the list.

(Comment 9) One comment asserted that regardless of QIDP designation status, ''drugs intended to treat qualifying pathogens'' (which we assume to mean drugs intended to treat infections caused by qualifying pathogens) should be required to prove reduction in mortality or morbidity. The comment further asserted that clinical trials in anti-infective drugs for

qualifying pathogens should have mortality as the primary endpoint.

(Response) These concerns apply to approval standards for particular drugs, which are required to be safe and effective within the meaning of section 505 of the FD&C Act. These concerns do not apply to the subject matter of the proposed rule, which is the method for identifying qualifying pathogens and the resulting list. Thus, FDA considers them irrelevant to the present rulemaking and will make no changes to the rule as a result.

C. Comments on Previously Proposed Pathogens

(Comment 10) One comment suggested edits and new literature references to a paragraph in the preamble to the proposed rule pertaining to the analysis of Enterobacteriaceae. These references are:

- A 2013 article by M. Sjölund Karlsson et al., ''Outbreak of Infections Caused by *Shigella sonnei* with Reduced Susceptibility to Azithromycin in the United States,'' in *Antimicrobial Agents and Chemotherapy* (Ref. 4);
- a 2010 article by M. R. Wong et al., ''Antimicrobial Resistance Trends of *Shigella* Serotypes in New York City, 2006–2009,'' in *Microbial Drug Resistance* (Ref. 5); and
- a 2007 article by S. D. Alcaine et al., ''Antimicrobial Resistance in Nontyphoidal *Salmonella,''* in *Journal of Food Protection* (Ref. 6).

The comment also made reference to CDC's National Antimicrobial Resistance Monitoring System for Enteric Bacteria (NARMS), but did not include specific data from NARMS in the comment.

(Response) FDA appreciates the comment and suggested literature references in support of FDA's decision to add Enterobacteriaceae to the list of qualifying pathogens. We agree that the three suggested literature references provide additional support for the inclusion of Enterobacteriaceae on the list of qualifying pathogens. Specifically, FDA agrees that the Karlsson and Wong references support recognition of an increase in *Shigella* resistance in the United States, and that the Alcaine reference supports recognition of an increase in *Salmonella* resistance. FDA thus incorporates these references as part of its basis for designating species in the Enterobacteriaceae family as qualifying pathogens. The comment did not provide specific NARMS data or specific references presenting relevant NARMS data, but rather made general reference to the surveillance project. FDA, thus, declines to incorporate the NARMS database in its entirety as part of its basis for designating species in the Enterobacteriaceae family as qualifying pathogens.

(Comment 11) Two comments made suggestions in response to FDA's inclusion of *Clostridium difficile* on the list of qualifying pathogens. One advocated improvements in hospital hygiene (e.g., hand washing) and staffing to reduce the spread of *C. difficile.* The other advocated an unidentified procedure for treatment of *C. difficile* and expressed concerns that the proposed rule would inhibit the use of this treatment.

(Response) FDA responds by thanking the commenters for their input. The proposed rule, however, describes the Agency's methodology for identifying qualifying pathogens and developing the resulting list. The propose rule does not address matters on hospital hygiene standards and non-pharmacologic procedures. Therefore, FDA will make no changes to the rule in response to these comments.

(Comment 12) One comment suggested adding *Mycobacterium abscessus* to the list of qualifying pathogens.

(Response) *M. abscessus* is a species of non-tuberculous mycobacteria, a category of pathogens already on the proposed list of qualifying pathogens in FDA's June 2013 proposed rule. As described in the proposed rule, FDA believes that non-tuberculous mycobacteria (including *M. abscessus*) meet the statutory standards for identification as ''qualifying pathogens,'' and this final rule adds non-tuberculous mycobacteria (including *M. abscessus*) to the list of qualifying pathogens (see 78 FR 35155 at 35163).

(Comment 13) One comment suggested adding *Proteus mirabilis* to the list of qualifying pathogens.

(Response) *P. mirabilis* is a species in the Enterobacteriaceae family, a category of pathogens already on the proposed list of qualifying pathogens in FDA's June 2013 proposed rule (see 78 FR 35155 at 35161). As described in the proposed rule, FDA believes that Enterobacteriaceae (including *P. mirabilis*) meet the statutory standards for identification as ''qualifying pathogens,'' and this final rule adds Enterobacteriaceae (including *P. mirabilis*) to the list of qualifying pathogens.

(Comment 14) One comment stated that ''poor adherence to therapy, overuse of currently available therapy, and empiric use'' should not be used in support of identifying a pathogen for inclusion on the list of qualifying pathogens—particularly *M. tuberculosis*—because these ''relate to clinical practice.''

(Response) FDA considers antibiotic stewardship and attention to patient adherence to therapy as important factors in determining transmissibility. FDA explained in the preamble to the proposed rule (see 78 FR 35155 at 35157) that a pathogen's ease of transmission is an important consideration in evaluating ''the impact on the public health due to drug-resistant organisms in humans'' (section 505E(f)(2)(B)(i) of the FD&C Act). This factor is one of the four statutory factors identified in section 505E(f)(2)(B)(i) of the FD&C Act. Therefore, FDA will make no changes to the rule in response to this comment.

D. Suggestions for Additional Qualifying Pathogens

(Comment 15) *Bacteroides, Fusobacterium,* and *Prevotella* Species

One comment suggested adding *Bacteroides, Fusobacterium,* and *Prevotella* species to the list of qualifying pathogens.

(Response) For the reasons that follow, FDA will not add these species to the list of qualifying pathogens. A discussion of these three bacterial pathogens is provided together for the following reasons: (1) These bacterial pathogens are representative of a group of medically-important gram-negative anaerobic rods (see Ref. 7 at pp. 3111–3120) and (2) common taxonomic characteristics (Ref. 8 at pp. 179–194).

These bacterial pathogens are commonly found in the mucous membranes (Ref. 9), particularly in the mouth (*Bacteroides, Fusobacterium,* and *Prevotella*), intestines (*Bacteroides*), and female urogenital tract (*Bacteroides, Fusobacterium,* and *Prevotella*) (Ref. 7 at p. 3112). Each of these bacterial pathogens can cause the same infectious diseases and are often implicated in odontogenic infections (particularly for those with poor dental hygiene or periodontal disease, as these bacteria populate dental plaque), peritonsilar infections, and polymicrobial abdominal infections, among others. Particularly when introduced into compromised tissue (e.g., via a wound or break in mucous membranes), these pathogens can cause abscesses that may require drainage or debridement in addition to antimicrobial therapy (Ref. 7 at p. 3117). Infection prevention is often the focus for these pathogens—either via ''avoiding conditions that reduce the redox potential of the tissues'' or

preventing the bacteria from entering wounds, often by administering prophylactic antimicrobial agents prior to surgery or dental work (Ref. 9).

In general, infections from these pathogens are not transmitted from one person to another or acquired from the environment, but rather occur from a person's own mucosal flora (id.). These infections, once established, are generally able to be treated successfully with surgical incision and drainage as well as administration of antimicrobial agents and treatment of underlying comorbid conditions (Ref. 7 at pp. 3111–3119 and Ref. 10). There have been reports of increases in the incidence of bacteremia caused by anaerobic pathogens (a classification that includes *Bacteroides, Fusarium,* and *Prevotella* species) (Ref. 11). However, these increases appear more likely to reflect the complex patient populations studied (id. at p. 898) rather than, for example, underlying changes in the species' transmissibility, pathogenicity or other characteristics that would likely signal a potential for meaningful increase in colonization rates or active infections.

Resistance to antimicrobial agents has been reported in the species of these genera, however (Ref. 9). For example, plasmid-mediated resistance has been seen in *Bacteroides* species (id.). Beta-lactamase production has been seen in *Bacteroides* species (see Refs. 12 and 13) and in *Prevotella* isolates (albeit less frequently than in *Bacteroides* isolates); *Fusobacterium* species have the lowest incidence of beta-lactamase production of the three genera (Refs. 12, 13, 14, and 15). Resistance to clindamycin and cefoxitin also has been noted in all three genera (Ref. 15). Nevertheless, while there have been suggestions of increasing resistance over time (Ref. 16), and while there is some concern regarding rates of resistance to penicillin and clindamycin, these bacteria still remain susceptible to many drugs (Refs. 12, 13, and 14). Furthermore, persuasive clinical data that may indicate poorer outcomes for resistant infections are lacking.

Taken together, the available data do not provide a compelling rationale for concluding that *Bacteroides, Prevotella,* or *Fusobacteria* species have the potential to pose a serious threat to public health within the meaning of the statute. Thus, FDA declines to include them on the list of qualifying pathogens at this time.

(Comment 16) *Brucella* Species

One comment suggested adding *Brucella* species to the list of qualifying pathogens.

(Response) Unlike the pathogens previously proposed as qualifying pathogens, *Brucella* infections remain susceptible to and may be treated by existing antibacterial drugs. Further, the incidence and prevalence of brucellosis is low enough that *Brucella* species are unlikely to pose a serious threat to public health—even if resistance were to emerge. Thus, for these reasons and those that follow, FDA declines to identify *Brucella* species as qualifying pathogens.

Bacteria of the genus *Brucella* are gram-negative coccobacilli that typically colonize animals (Ref. 7 at p. 2921). Rarely, certain *Brucella* species (most frequently *B. melitensis*) may infect humans. In these cases, infection often occurs when broken human skin comes in contact with infected animals or animal fluids, when a person inhales aerosolated bacteria, or when a person consumes unpasteurized dairy products (id.). Brucellosis generally causes nonspecific constitutional symptoms (e.g., malaise, fever, headache, anorexia) and can cause more serious arthritis, central nervous system infection, and hepatitis, among other conditions and symptoms (Ref. 7 at p. 2922). *Brucella* infections are usually not transmitted person-to-person (Ref. 7 at p. 2921); therefore, the people at highest risk of *Brucella* infections include those who consume unpasteurized dairy products or who work with animals or the bacteria itself: Ranchers, veterinarians, lab researchers, and slaughterhouse workers, i.e., isolated environmental exposures (id.).

The incidence of human brucellosis remained stable from 1990 to 2003 (Ref. 17), increased from 2003–2007, and decreased by 36 percent in 2008 (Ref. 18). FDA is aware of no data that suggest a meaningful post-2008 increase in *Brucella* infection in humans—to the contrary, recent data suggest that infections have decreased from 2012 to 2013 (Ref. 19 at Table 1)—and the overall prevalence of brucellosis remains low in the United States (Ref. 7 at p. 2921). *Brucella* species have been listed as a category B (second-highest priority) bioterrorism threat on CDC's list of bioterrorism agents (Ref. 20), but this classification takes into account such elements as ease of dissemination of the pathogen (e.g., it can be aerosolized) in a bioterrorism setting, and the need for CDC's enhancement of diagnostic and surveillance capabilities (id.). Importantly, this classification also recognizes that brucellosis causes only ''moderate morbidity rates and low mortality rates'' (id.). Indeed, although brucellosis may require long courses of treatment (e.g., 6 weeks or more) and can involve tissue sites that enhance the difficulty of treatment (e.g., central nervous system infection), the prognosis for *Brucella* infection is generally favorable with appropriate treatment (Ref. 21).

Treatment recommendations for brucellosis have remained unchanged for many years and include the use of tetracycline or doxycycline plus gentamycin, or doxycycline plus rifampin (id.). Despite occasional overseas reports of resistance (Refs. 22 and 23), *Brucella* species generally remain susceptible to the mainstays of brucellosis treatment, even abroad (Refs. 24, 25, 26, and 97). In FDA's view, the currently available data do not demonstrate widespread antimicrobial resistance in *Brucella* infections, nor do they support the potential for a meaningful increase in drug resistance for *Brucella* species.

Thus, for the foregoing reasons, FDA will not identify *Brucella* species as qualifying pathogens.

(Comment 17) *Clostridium* Species Other Than *C. difficile*

One comment suggested adding *Clostridium* species other than *C. difficile* to the list of qualifying pathogens.

(Response) For the reasons that follow, FDA declines to add non-*difficile Clostridium* species to the list of qualifying pathogens.

There are over 200 non-*difficile* species of the bacterial genus *Clostridium.* These toxin-producing, anaerobic rods are found in soil and in normal human and animal flora, and often infect or intoxicate humans via contaminated food or wounds (Ref. 7 at p. 3103), although mother-to-child transmission has been identified for such pathogens as *C. tetani.* These pathogens cause a variety of diseases or conditions, including: Food poisoning (*e.g., C. perfringens*), including botulism (*C. botulinum*); tetanus (*C. tetani*); clostridial myonecrosis, also called gas gangrene (*C. perfringens*); bloodstream infections (*C. perfringens* and *C. septicum)* (Ref. 7 at pp. 3091–3092, 3097–3098, 3106–3107); and, less commonly, toxic shock syndrome (*C. sordellii*) (Ref. 27).

Non-*difficile Clostridium* outbreaks are reported from time to time (Ref. 28), but foodborne *C. perfringens* infections are the most common, causing approximately 1 million cases of mostly mild to moderate gastroenteritis in the United States each year (Ref. 29). *C. perfringens* often colonizes meat or poultry, and illness may result from large volumes of food kept warm for a long period of time (e.g., in buffets) (id.)

or in outbreaks associated with particular prepared foods (Refs. 30 and 31). *C. botulinum,* which also causes food poisoning, is relatively rare, though much more severe—it is likely fatal if untreated (Refs. 29 and 32), whereas *C. perfringens* infections are often self-limited and require simply oral rehydration and supportive care at home. Other *Clostridium*-related diseases, such as tetanus, bloodstream infections, and gas gangrene, are life-threatening and require immediate treatment.

Some infections caused by *Clostridium* species are very rare. For example, less than 200 cases of botulism were reported annually to the CDC, and less than 50 cases of tetanus were reported annually to the CDC, in each of the past 5 years (Ref. 19). While CDC does not require reporting of other clostridial infections, antimicrobial susceptibility studies ''have not changed significantly over the past 10 years'' (Refs. 19 and 33).

In contrast with *C. difficile, C. perfringens* is not transmitted from human to human (Refs. 34, 35, and 36),[2] and FDA is unaware of significant increases in incidence or prevalence of infections with *C. perfringens* or other non-*difficile Clostridium* pathogens.

There have been reports of limited antimicrobial resistance in non-*difficile Clostridium* species (Refs. 15, 37, 38, 39, and 40), and studies have found that resistance genes may (or may potentially) be transferred between *C. perfringens* species (Refs. 41 and 42). However, many reports of resistant isolates do not offer a correlation either with resistant infections seen in a clinical setting (Ref. 40) or with suggestions of worse outcomes in patients with resistant infections (Ref. 39) (particularly for *C. perfringens,* whose infections rarely require treatment, and for which antibacterial therapy is not recommended). Many therapies still remain available and effective for treating the more severe non-*difficile Clostridium* infections, and, limited in vitro resistance reports notwithstanding, FDA has not seen evidence that there is a strong potential for a meaningful increase in resistance rates in these pathogens.

For the foregoing reasons—and particularly when contrasted with the considerations described in the proposed rule pertaining to *C. difficile*—FDA does not believe there are sufficient data available to find that non-*difficile Clostridium* species meet the statutory standard for listing as qualifying pathogens. Thus, FDA will not include these pathogens on the list of qualifying pathogens.

(Comment 18) *Coccidioides* Species

Six comments suggested adding *Coccidioides immitis* to the list of qualifying pathogens. Six comments suggested adding *C. posadasii* to the list of qualifying pathogens. One comment suggested adding *Coccidioides* species (generally) to the list of qualifying pathogens. According to the comments, *Coccidioides* species present a serious and growing public health concern, particularly in the southwestern United States.

(Response) FDA agrees with the comments and will include *Coccidioides* species on the list of qualifying pathogens.

Coccidioides species are pathogenic fungi that are endemic to certain regions of southwestern United States (i.e., certain areas of California, Arizona, New Mexico, Texas, Utah, and Nevada) and other regions of the Western Hemisphere (Ref. 7 at pp. 3333–3334). The pathogen is responsible for causing coccidioidomycosis, also known as Valley Fever, with *C. immitis* and *C. posadasii* as the causative agents. *Coccidioides* species is acquired via respiratory inhalation of spores.

Infections caused by *Coccidioides* species have increased in the past decade. It is estimated that up to 60 percent of people living in the endemic areas of southwestern United States have been exposed to the fungus (Ref. 43). According to a March 2013 report, the CDC found that more than 20,000 cases of Valley Fever are reported annually in the United States, but many cases go unreported (Ref. 44). Some researchers estimate that the fungus infects more than 150,000 people each year (Ref. 45). The CDC observed that the incidence of reported Valley Fever increased substantially between 1998 and 2011, from 5.3 per 100,000 people in the endemic area in 1998 to 42.6 per 100,000 in 2011 (Ref. 44). Although some of the increase can be attributed to changes in the case definition based on serologic evidence of infection (Ref. 46), the incidence of infections caused by the fungi continued to increase even after taking into account the change in the case definition. Notably, the CDC found that the incidence of reported Valley Fever increased in Arizona and California from 2009 to 2010 and from 2010 to 2011 (Ref. 44).

Of the infections, one-half to two-thirds are subclinical (Ref. 45). Symptomatic patients typically experience a self-limited acute or subacute community-acquired pneumonia that becomes evident 1 to 3 weeks after infection (id.), with fever, cough, headache, rash, muscle aches, and joint pain as typical symptoms (Ref. 47). Some patients develop severe or chronic pulmonary disease, and less than one percent of patients experience extrapulmonary infection (Ref. 44). Chronic pulmonary or disseminated disease can occur months or years after the initial infection (Ref. 48). For extrapulmonary disease (also referred to as disseminated disease), estimates range as high as 30 to 50 percent of ''infections for heavily immunosuppressed patients, such as those with AIDS, lymphoma, receipt of a solid-organ transplant, or receipt of rheumatologic therapies, such as high-dose corticosteroids or anti-tumor-necrosis-factor (TNF) medications'' (Ref. 45).

In a 2007 to 2008 population-based study in Arizona, over 40 percent of patients with Valley Fever required hospitalization, and symptoms lasted a median of 120 days (Ref. 49). Furthermore, between 1998 to 2008, the annual number of coccidioidomycosis-related deaths was about 163, with the highest risk of death associated with men, persons aged 65 or greater, Hispanics, Native Americans, and residents of Arizona or California (Ref. 50).

Resistance mechanisms for *Coccidioides* species have not been identified (Ref. 51). There is evidence of at least one report of resistance to the azole class of antifungal agents (id.). In a retrospective analysis of patients presenting with coccidioidal meningitis at Los Angeles, CA, hospitals, researchers found that a significant proportion of patients—40 percent—died, despite treatment with fluconazole monotherapy or a combination of fluconazole and intravenous amphotericin B (Ref. 52). Therefore, it is plausible that resistance has increased given the increase in the rate of growth of Valley Fever.

For the reasons stated previously, FDA believes that *Coccidioides* species has the potential to pose a serious threat to public health, and FDA is including *Coccidioides* species on the list of qualifying pathogens.

(Comment 19) *Cryptococcus* Species

Two comments suggested adding *Cryptococcus* species to the list of qualifying pathogens due to, among other things, *C.gattii* infections in North America and concerns about worldwide morbidity and mortality from cryptococcal infections generally.

(Response) For the reasons that follow, FDA will include these species as qualifying pathogens.

[2] *See* 78 FR 35155 (June 12, 2013).

Cryptococcus species are encapsulated yeast fungi (Ref. 7 at p. 3287). Although there are 19 species in the genus (Ref. 7 at p. 3287), *C. neoformans* and *C. gattii* are the two generally associated with human disease (Ref. 7 at pp. 3288–3289). Both species are found in soil, and infection typically occurs via inhalation of the fungi (Ref. 7 at p. 3290). Cryptococcal disease often presents as lung or central nervous system disease (Ref. 7 at p. 3293), although the pathogens also can infect other parts of the body (Ref. 53).

Most *C. neoformans* occur in immunocompromised patients (Ref. 7 at p. 3289), and *C. neoformans* meningitis cases are very rare in healthy people, with an incidence of only 0.4 to 1.3 per 100,000 people (Ref. 54). Incidence of cryptococcal disease increased substantially with the HIV/AIDS epidemic in the late portion of the 20th century and remains high in developing countries, where antiretroviral therapy is scarce (id.). In developed countries, the use of antiretroviral therapy has reduced the number of end-stage HIV/AIDS patients susceptible to cryptococcal infection (Ref. 55); incidence rates in this population in the United States are between 2 and 7 infections per 100,000 people (Ref. 54). Although HIV/AIDS-related cryptococcosis is declining, an increasing population (Ref. 53) of immunosuppressed patients—including solid organ transplant patients, cancer patients, and patients on corticosteroids—remain at risk of *C. neoformans* infections (Ref. 56). Non-HIV patients appear to bear an increasing burden of cryptococcal disease, representing 16 percent of all U.S. cryptococcal meningitis cases in 1997 but 29 percent of all U.S. cryptococcal meningitis cases in 2009 (Ref. 55). Cryptococcosis is the third most common invasive fungal infection in solid organ transplant patients after candidiasis and aspergillosis (Ref. 56).

C. gattii infections, however—which had been considered geographically limited to areas such as Australia and New Zealand because of an association with eucalyptus trees (Ref. 57)—have become an increasing public health concern for healthy, rather than immunocompromised, people in North America. Although *C. gattii* infections also have been documented in HIV patients, ''[t]he emergence of *C. gattii* infections in immunocompetent human and animal populations in the Pacific Northwest region of North America is nothing short of remarkable'' (Ref. 56). After an initial outbreak on Vancouver Island in 1999, incidence rates of *C. gattii* infections were estimated to be 37 times higher than in the endemic areas of Australia and New Zealand (Ref. 53). A retrospective analysis in the Pacific Northwest area of the United States did not identify any patients with cryptococcal infection due to *C. gattii* before 2000 (Ref. 58), while 100 infections were documented in the United States between 2004 and 2011, mostly from the Pacific Northwest area of the United States (Ref. 98).

Both *C. neoformans* and *C. gattii* can cause life-threatening infections, although the primary infection sites may differ. For example, in the initial Vancouver Island outbreak of *C. gattii* infections about 70 percent of patients had lung disease (Ref. 53), and in *C. neoformans* infections in immunocompromised patients (who comprise the majority of those infected), meningitis or other central nervous system disease is the most common presentation of infection (id.). Those *C. gattii* patients who have central nervous system involvement may have more neurological sequelae than *C. neoformans* patients, however (id.). These sequelae may require longer courses of antifungal therapy to treat (id.), and may result in permanent neurological damage (Ref. 59). Regardless of interspecies disease differences, infection with either pathogen is likely to be very serious. In one study of *C. gattii* infections, 91 percent of infected patients were hospitalized and 33 percent died (Ref. 60). Mortality rates for *C. neoformans* infections are approximately 12 percent in developed countries, and that rate rises to 50 to 70 percent in sub-Saharan Africa, where treatment is less accessible (Ref. 54).

According to one set of clinical practice guidelines, ''[c]ryptococcosis remains a challenging management issue, with little new drug development or recent definitive studies'' (Ref. 61). Both pathogens require long courses of antifungal therapy for treatment, although the success and components of therapy may differ somewhat depending on the primary site of infection and the immunological competence and underlying condition of the patient (id.). In recent years, however, studies on both pathogens have indicated signs of increasing resistance to antifungal therapies. For example, according to a 10-year ARTEMIS Global Antifungal Surveillance Program (ARTEMIS) survey, the proportion of *C. neoformans* isolates showing resistance to fluconazole increased from 7.3 percent in 1997–2000 to 11.7 percent in 2005–2007 (Ref. 62). Furthermore, in one study, *C. gattii* isolates from the Pacific Northwest were more resistant to antifungal drugs than non-Pacific Northwest *C. gattii* isolates or *C. neoformans* isolates (Ref. 63). This result supports the observation that infection with *C. gattii* strains from the Pacific Northwest may result in worse clinical outcomes than infection with other *C. gattii* strains (e.g., a 33 percent mortality rate seen in Pacific Northwest infections versus a 13 percent mortality rate seen in infections in Australia) (id.).

In sum, evidence of increasing resistance combined with increases in immunocompromised patients, the emergence of *C. gattii* infections in the Pacific Northwest in healthy individuals, and the seriousness of cryptococcal disease, have led FDA to conclude that *Cryptococcus* species have the potential to pose a serious risk to public health. FDA thus will add these pathogens to the list of qualifying pathogens.

(Comment 20) *Fusarium* Species

One comment suggested adding *Fusarium* species to the list of qualifying pathogens because the fungal agent causes serious and life-threatening infections.

(Response) Preliminarily, FDA notes that the comment appears to have conflated the standards for qualifying pathogens (''*pathogen[s] . . .* that ha[ve] the *potential* to pose a *serious threat to public health''* (section 505E(f) of the FD&C Act)) and QIDPs (certain human ''*drugs . . .* intended to treat *serious or life-threatening infections''* (section 505E(g) of the FD&C Act)) (emphasis added). For the reasons that follow, FDA declines to add *Fusarium* species to the list of qualifying pathogens.

Fusarium species are fungi found mainly as saprophytic organisms in soil. Since the 1970s, the number of reports of human infection due to *Fusarium* species has increased, mainly involving immuocompromised patients (Ref. 7 at p. 3369). Infections caused by *Fusarium* species occur most commonly in patients with acute leukemia and prolonged neutropenia (id.). The fungi can cause localized infection, deep-seated skin infections, and disseminated disease. The rare cases of disseminated disease have been reported in the clinical settings of severe burns, trauma, and heat stroke (id.). Reports of localized infection in patients without leukemia or prolonged neutropenia are infrequent and usually involve the skin (e.g., complication of a burn) or ocular tissues (Ref. 64).

Inhalation, ingestion, and entry through skin trauma have been suggested as the portal of entry (Ref. 7 at p. 3369). More recently, water has also been suggested as a source of these

infections, as the fungus was found in one hospital water supply system and in several water sources at a dialysis clinic (id.). Infection commonly presents with fever and myalgia not responsive to antibacterial therapy during periods of profound neutropenia (id). Skin lesions occur in 60 to 80 percent of infections and can occur within 1 day of the onset of fever (id.). Overall mortality in this infection has been reported to be between 50 to 80 percent (Ref. 7 at p. 3370). Survival is generally associated with the recovery from neutropenia (id.). The high rates of morbidity and mortality are usually due to the patients' underlying immune suppression and prolonged neutropenia (Ref. 65).

Generally, while susceptibility varies among *Fusarium* species, susceptibility to antifungal drugs generally is thought to be low (Ref. 7 at p. 3370). The management of fusariosis almost always includes surgical debridement, so it is often difficult to ascertain the role of antifungal drugs versus the role of surgical debridement when considering the outcomes of patients with this infection (Ref. 65).

While *Fusarium* species is associated with high morbidity and mortality rates, there do not appear to be new or changing public health concerns with infections caused by this fungi. Although antifungal therapy plays a role, the standard of care is focused on surgical debridement and reestablishment of the patient's immune system. Therefore, FDA will not be adding *Fusarium* species to the list of qualifying pathogens.

(Comment 21) *Helicobacter Pylori*

One comment suggested adding *Helicobacter pylori* to the list of qualifying pathogens because the pathogen is a major cause of morbidity, specifically a range of gastroduodenal diseases.

(Response) For the reasons that follow, FDA is adding *H. pylori* to the list of qualifying pathogens.

H. pylori is a gram-negative bacterium that survives in the gastric epithelium or mucosal layer and occasionally in the duodenal or esophageal mucosal epithelium. *H. pylori* is one of the most common bacterial pathogens, estimated to infect about 60 percent of the world's population (Ref. 66).

About 20 percent of infected individuals develop gastroduodenal disorders in their lifetime (Ref. 67). For symptomatic individuals, *H. pylori* can cause severe gastric disease, including: Gastritis, duodenal and gastric ulcers, duodenal and gastric cancers, and mucosal-associated-lymphoid-type (MALT) lymphoma (Ref. 68). Approximately 15 percent of infected people will develop a peptic ulcer, and 1 to 3 percent will develop a gastric malignancy during their lifetime (Ref. 69). Persons infected with *H. pylori* also have a two- to six-times greater risk of developing gastric cancer and MALT lymphoma compared with uninfected individuals (Ref. 68).

Transmission occurs fecal-oral, gastric-oral, or oral-oral from human-to-human contact (Ref. 70). Risk factors include poor socioeconomic conditions, family overcrowding, poor hygiene, and living with an infected family member (id.). Incidence of new infections in developing countries is 3 to 10 percent of the population each year, compared to 0.5 percent in developed countries, due predominantly to better hygiene practices (id.). In the United States, age-adjusted prevalence of *H. pylori* is higher in Mexican-Americans at 62 percent and non-Hispanic blacks at 53 percent, compared to non-Hispanic whites at 26 percent (Ref. 71).

H. pylori antibiotic resistance has been widely reported at a global level. Resistance mechanisms against antibacterial drugs used to treat *H. pylori* infections have been identified (Ref. 72). For metronidazole, ''high intracellular redox potential of aerobe species prevents the metronidazole reduction-activation and is responsible for the intrinsic resistance'' (id.). Prevalence of antibacterial resistance varies in different geographic regions, and it has been correlated with the consumption of antibacterial drugs in the general population (Refs. 73 and 74).

A retrospective analysis of 31 worldwide studies concerning *H. pylori* published between January 2006 and December 2009 showed substantial rates of antibacterial drug resistance (Ref. 73). For example, 9.6 percent of worldwide *H. pylori* isolates showed resistance to two or more antibacterial drugs. A U.S. network of clinical sites that tracked national prevalence rates of *H. pylori,* called the *Helicobacter pylori* Antimicrobial Resistance Monitoring Program, identified 347 clinical isolates of *H. pylori* to be analyzed for resistance to antibacterial drugs (Ref. 67). The researchers observed that 29.1 percent of isolates were resistant to one antibacterial drug and 4.8 percent of isolates were resistant to two or more antibacterial drugs. Other regions, such as China (Ref. 75) and Africa (Ref. 73), have reported even greater resistance rates to antibacterial drugs. Resistance to some classes of antibacterial drugs was associated with a reduction in treatment efficacy (Ref. 76). Eradication of *H. pylori* in humans is being challenged by the increasing rates of resistance to current treatment (Ref. 77). For the reasons described previously, FDA believes that *H. pylori* has the potential to pose a serious threat to public health, and FDA will add *Helicobacter pylori* to the list of qualifying pathogens.

(Comment 22) *Pandoraea* Species

One comment suggested adding *Pandoraea* species to the list of qualifying pathogens.

(Response) For the reasons that follow, FDA declines to add *Pandoraea* species to the list of qualifying pathogens.

The *Pandoraea* bacterial genus was identified in 2000; as of 2011, it contained five species (Ref. 78), all of which are aerobic gram-negative rods (Ref. 79). Historically, proper identification of these bacteria has been a challenge (id.), although a recent poster presentation at an international meeting suggested that *Pandoraea* species' production of carbapanem-cutting oxacillinase enzymes (which suggests that these bacteria may have intrinsic resistance to carbapanem antibiotics) may be a useful diagnostic tool (id.).

These bacteria are generally opportunistic and tend to colonize or infect patients with cystic fibrosis (CF) in particular (Ref. 78). However, both the prevalence and the pathogenic role of *Pandoraea* bacteria in patients with CF are unknown (Ref. 80). There have been reports of sporadic *Pandoraea*-related bacteremia and lung infections, including some in non-CF patients (Ref. 78). In addition, a 2003 report describes six CF patients who acquired *Pandoraea species* infections and four (out of the six) patients subsequently experienced a decline in lung function (Ref. 81).

Currently, there is too little information available about *Pandoraea* species to support their inclusion on the list of qualifying pathogens. Aside from a suggestion of intrinsic carbapanem resistance (Ref. 79), FDA is unaware of data suggesting increasing resistance—or any acquired resistance—to available therapies, or poorer outcomes with resistant strains of these pathogens. Further, ''[t]he clinical significance of colonization with these organisms remains unclear, and there are limited and conflicting data available on the clinical outcome of patients colonized with *Pandoraea''* (Ref. 78). Thus, FDA declines to add *Pandoraea* species to the list of qualifying pathogens at the present time.

(Comment 23) *Peptostreptococcus* Species

One comment suggested adding *Peptostreptococcus* species to the list of qualifying pathogens.

(Response) For the reasons that follow, FDA declines to add *Peptostreptococcus* species to the list of qualifying pathogens.

The *Peptostreptococcus* genus consist of anaerobic, gram-negative bacteria that are a part of the normal flora of human mucocutaneous surfaces, including the mouth, gastrointestinal track, female genitourinary system, urethra, and skin (Ref. 7 at p. 3121). The bacteria can cause a wide variety of infections, including respiratory, oropharyngeal, sinus, ear, musculoskeletal, intraabdominal, genitourinary, cardiovascular, dental, superficial, and soft tissue infections (Ref. 82). Infection typically is associated with trauma or disease (Ref. 83 at pp. 309–312) and has been identified to be a significant component of mixed infections (Ref. 82).

Notably, there is no evidence to show an increase in the rate of incidence or prevalence with *Peptostreptococci* (Ref. 84). Until recently, most clinical isolates of gram-positive anaerobic cocci were identified as a species of *Peptostreptococcus,* but this genus is currently being reclassified into three new genera: *Micromonas, Anaerococcus,* and *Peptoniphilus* (Ref. 85). Some species are also being transferred, for example, to the genus *Streptococcus* (Ref. 7 at p. 3121).

While resistance to antibacterial drugs is rare, resistance mechanisms have been identified as the transfer of plasmid-mediated mechanisms (Ref. 86 at p. 878). *Peptostreptococci* are usually fully susceptible to penicillin (Ref. 7 at p. 3122), though some isolates have occasionally been found to be resistant to penicillin (Ref. 85). Further, the genus has consistently reported no resistance to metronidazole, clindamycin, and imipenem (Ref. 84). Surveillance data from England and Wales do not support concerns regarding resistance to antibacterial therapies (Ref. 85).

There does not seem to be an emerging public health concern with infections caused by *Peptostreptococci.* Although resistance mechanisms have been identified, data on clinical pathogens are lacking and the rates of incidence or prevalence have not been shown to be increasing. Therefore, FDA will not be including *Peptostreptococcus* on the list of qualifying pathogens.

(Comment 24) *Scedosporium* Species

One comment suggested adding *Scedosporium* species to the list of qualifying pathogens because the fungal agent causes serious and life-threatening infections.

(Response) FDA notes that the comment appears to have conflated the standards for qualifying pathogens (''*pathogen[s] . . .* that ha[ve] the *potential* to pose a *serious threat to public health''* (section 505E(f) of the FD&C Act)) and QIDPs (certain human ''*drugs . . .* intended to treat *serious or life-threatening infections''* (section 505E(g) of the FD&C Act)) (emphasis added). For the reasons that follow, FDA declines to add *Scedosporium* species to the list of qualifying pathogens.

Scedosporium comprises a family of fungi that is responsible for an increasing number of infections, particularly among immunocompromised patients (Ref. 87). Two species of *Scedosporium* are medically relevant: *S. apiospermum* and *S. prolificans.* These fungi are saprophytic agents with worldwide distribution that are isolated from natural sources (Ref. 88 at p. 4).

The fungi are typically acquired via direct inoculations, through a trauma wound or wound puncture (id.). *Scedosporium* infections are rare but can cause human infectious diseases, including soft tissue infections, septic arthritis, osteomyelitis, ophthalmic infections, sinusitis, pneumonia, meningitis and brain abscesses, endocarditis, and disseminated infection (Ref. 89). Disseminated infection has been observed with both species of *Scedosporium* (Ref. 88 at p. 4).

The overall incidence of *Scedosporium* infections is relatively low in most geographic areas of the United States. Hospital-based infections in patients with hematological malignancies have been observed (Ref. 87). Most disseminated *S. prolificans* infections are fatal due to persistent neutropenia and the intrinsic resistance to available antifungal agents (Ref. 90). Additionally, the management of invasive *S. apiospermum* infections is difficult because the pathogen has intrinsic resistance to many antifungal agents, including fluconazole and amphotericin (Ref. 91). A combination of chemotherapy and surgery seems to be the best approach in treating the infection (Ref. 88). Recovery from disseminated *Scedosporium* infections appears to result from improvement of the underlying disease (e.g., recovery from neutropenia) rather than from antifungal treatments (id.). Therefore, rate of growth of resistant organisms and an evaluation of rates of resistance would not provide meaningful evidence to support inclusion on the list of qualifying pathogens.

While *Scedosporium* is associated with high morbidity and mortality, the incidence of disease associated with *Scedosporium* is rare, and therefore there do not appear to be new public health concerns with these infections. For these reasons, FDA will not add *Scedosporium* to the list of qualifying pathogens.

(Comment 25) Zygomycetes (*Mucor, Rhizopus, Absidia, Cunninghamella*)

One comment suggested adding Zygomycetes (specifically, *Mucor, Rhizopus, Absidia,* and *Cunninghamella*) to the list of qualifying pathogens because these fungal agents cause serious and life-threatening infections.

(Response) FDA notes that the comment appears to have conflated the standards for qualifying pathogens (''*pathogen[s] . . .* that ha[ve] the *potential* to pose a *serious threat to public health''* (section 505E(f) of the FD&C Act)) and QIDPs (certain human ''*drugs . . .* intended to treat *serious or life-threatening infections''* (section 505E(g) of the FD&C Act)) (emphasis added). For the reasons that follow, FDA declines to add Zygomycetes to the list of qualifying pathogens.

The class of Zygomycetes is a large group of fungi that are mostly opportunistic pathogens responsible for infections in high-risk patients, such as immunocompromised and type 2 diabetes mellitus patients (Ref. 92). There are two orders of Zygomycetes of medical interest: the *Mucorales,* which cause the majority of illness, and the *Entomophthorales* (Ref. 93 at p. 236). The main categories of human disease associated with *Mucorales* are sinusitis/rhinocerebral, pulmonary, cutaneous/subcutaneous, gastrointestinal, and disseminated zygomycosis (Ref. 93 at p. 244).

The host generally acquires the infectious spores through inhalation, ingestion, or inoculation through breaches in or penetrating injuries to the skin (Ref. 92). Host risk factors include diabetes mellitus, neutropenia, sustained immunosuppressive therapy, broad-spectrum antibiotic use, severe malnutrition, and primary breakdown in the integrity of the cutaneous barrier such as trauma, surgical wounds, needle sticks, or burn wounds (id.). Zygomycosis occurs rarely in non-immunocompromised hosts.

Zygomycetes are relatively uncommon isolates in the clinical

laboratory and are less frequent than invasive fungi caused by *Aspergillus* species. According to one report, ''[i]ncidence figures are difficult to collect as few national studies have been undertaken, but for the United States, the annual incidence of zygomycosis has been estimated as 1.7 infections per million people'' (Refs. 92 and 94). According to a 2002 report, the incidence of zygomycosis may be increasing; researchers found an increase in the number of hematopoietic stem cell transplant recipients at the Fred Hutchinson Cancer Center in Seattle, WA, infected with Zygomycetes from 1985–1989 to 1995–1999 (Ref. 95). Another study found that invasive fungal infections due to Zygomycetes were associated with higher mortality rates in adult hematopoietic stem cell transplant recipients at 64.3 percent, with suboptimal therapeutic modalities for the management of the infection as one contributing factor to the high rates (Ref. 96).

Surgical debridement should be considered as an option early in management of zygomycosis as the evidence indicates that this intervention improves survival (Ref. 92). Additionally, the agent of choice was conventional amphotericin B used at higher than normal doses (id.). FDA's research did not identify any papers that suggest an increase in the resistance rates to antifungal treatment.

Zygomycetes are associated with high morbidity and mortality rates. However, there do not appear to be new or changing public health concerns with infections caused by Zygomycetes. Further, resistance data on clinical pathogens are lacking. Therefore, FDA will not add Zygomycetes to the list of qualifying pathogens.

IV. 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.

V. Analysis of Economic Impact

A. Final Regulatory Impact Analysis

FDA has examined the impacts of the final 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 final 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 final 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 certifies that the 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 $141 million, using the most current (2013) Implicit Price Deflator for the Gross Domestic Product. FDA does not expect this final 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 antibacterial or antifungal 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 that 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 antibacterial or antifungal drugs, Congress enacted the GAIN title of FDASIA to create an incentive system. The primary framework for encouraging antibacterial or antifungal drug development became effective on July 9, 2012, through a self-implementing provision that authorizes FDA to designate human antibacterial 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 antibacterial 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 March 12, 2014, FDA granted 41 QIDP designations. As explained above, 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 final 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 final rule identifies 21 ''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 final 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 on 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 on 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 also would 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 on 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 final rule reflect not only current thinking regarding the types of pathogens that 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 final rule, this final 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.

VI. Paperwork Reduction Act

FDA concludes that this 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 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.

VII. Federalism

FDA has analyzed this rule in accordance with the principles set forth in Executive Order 13132. FDA has determined that the rule does 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 concludes that this 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.

VIII. 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, but FDA is not responsible for any subsequent changes to the 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 added 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. 355f, 371.

§ 317.1 [Reserved]

§ 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) *Coccidioides* species.
(h) *Cryptococcus* species.
(i) Enterobacteriaceae.
(j) *Enterococcus* species.
(k) *Helicobacter pylori.*
(l) *Mycobacterium tuberculosis* complex.

(m) *Neisseria gonorrhoeae.*
(n) *Neisseria meningitidis.*
(o) Non-tuberculous mycobacteria species.
(p) *Pseudomonas* species.
(q) *Staphylococcus aureus.*
(r) *Streptococcus agalactiae.*
(s) *Streptococcus pneumoniae.*
(t) *Streptococcus pyogenes.*
(u) *Vibrio cholerae.*

Dated: May 29, 2014.

Leslie Kux,

Assistant Commissioner for Policy.

[FR Doc. 2014–13023 Filed 6–4–14; 8:45 am]

BILLING CODE 4160–01–P

DEPARTMENT OF STATE

22 CFR Part 42

[Public Notice: 8755]

RIN 1400–AD52

Visas: Documentation of Immigrants Under the Immigration and Nationality Act, as Amended

AGENCY: Department of State.

ACTION: Final rule.

SUMMARY: Pursuant to the Violence Against Women and Department of Justice Reauthorization Act of 2005, the Department of State amends the immigrant visa classification table listed in the Department's regulations to add a symbol for an immigrant visa issued to to an alien who: is the parent of a current U.S.citizen, or the parent of a former U.S. citizen who, within the two-year period prior to filing the petition, lost or renounced U.S. citizenship status related to an incident of domestic violence or died; is a person of good moral character; is eligible to be classified as an immediate relative under the Immigration and Nationality Act; resides, or has resided, with the U.S. citizen daughter or son; demonstrates that he or she has been battered or subject to extreme cruelty by the U.S. citizen daughter or son; and has an approved petition from the Department of Homeland Security.

DATES: This rule becomes effective June 5, 2014.

FOR FURTHER INFORMATION CONTACT: Taylor W. Beaumont, Department of State, Bureau of Consular Affairs, Office of Visa Services, Legal Affairs, Division of Legislation and Regulations, 600 19th Street NW., Washington, DC 20431, email (*BeaumontTW@state.gov*).

SUPPLEMENTARY INFORMATION: Section 816 of the Violence Against Women and Department of Justice Reauthorization Act of 2005, Title VIII of Public Law 109–162, codified at 8 U.S.C. 1154(a)(1)(A)(vii), created an immigrant visa classification for the parents of U.S. citizens, and the parents of former U.S. citizens who, within the past two years, have lost or renounced U.S. citizenship status related to an incident of domestic violence or died.

The Department currently identifies applicants for this status using the ''IB5'' symbol, an existing symbol used for parents of U.S. citizens who are at least 21 years old. The unique IB5 classification symbol will facilitate the Department's ability to identify applicants for such status in various immigrant visa information databases.

Regulatory Findings

A. Administrative Procedure Act

Since this rule concerns the administration of visas, which is a foreign affairs function of the United States, the Department publishes this rule as a final rule pursuant to 5 U.S.C. 553(a)(1). In addition, since this rule implements the provisions of the Violence Against Women and Department of Justice Reauthorization Act of 2005, the Department finds that notice and public comment on this rule are unnecessary, pursuant to 5 U.S.C. 553(b)(B). Accordingly, this rule is effective immediately.

B. Regulatory Flexibility Act/Executive Order 13272: Small Business

Because this rule is exempt from notice and comment rulemaking under 5 U.S.C. 553, it is exempt from the regulatory flexibility analysis requirements set forth at sections 603 and 604 of the Regulatory Flexibility Act (5 U.S.C. 603 and 604). Nonetheless, consistent with section 605(b) of the Regulatory Flexibility Act (5 U.S.C. 605(b)), the Department has reviewed this regulation and certifies that this rule will not have a significant economic impact on a substantial number of small entities.

C. The Unfunded Mandates Reform Act of 1995

Section 202 of the Unfunded Mandates Reform Act of 1995, Public Law 104–4, 109 Stat. 48, 2 U.S.C. 1532, generally requires agencies to prepare a statement before proposing any rule that may result in an annual expenditure of $100 million or more by State, local, or tribal governments, or by the private sector. This rule will not result in any such expenditure, nor will it significantly or uniquely affect small governments.

D. The Small Business Regulatory Enforcement Fairness Act of 1996

This rule is not a major rule as defined by 5 U.S.C. 804, for purposes of congressional review of agency rulemaking under the Small Business Regulatory Enforcement Fairness Act of 1996, Public Law 104–121. This rule would not result in an annual effect on the economy of $100 million or more; a major increase in costs or prices; or significant adverse effects on competition, employment, investment, productivity, innovation, or on the ability of United States-based companies to compete with foreign-based companies in domestic and export markets.

E. Executive Order 12866

The Department does not consider this rule to be a ''significant regulatory action'' within the scope of section 3(f) of Executive Order 12866. Nonetheless, the Department has reviewed the rule to ensure its consistency with the regulatory philosophy and principles set forth in the Executive Order.

F. Executive Order 13563

The Department of State has considered this rule in light of Executive Order 13563 and affirms that this regulation is consistent with the guidance therein.

G. Executive Orders 12372 and 13132: Federalism

This regulation will not have substantial direct effects on the states, on the relationship between the national government and the states, or the distribution of power and responsibilities among the various levels of government. Nor will the rule have federalism implications warranting the application of Executive Orders 12372 and 13132.

H. Executive Order 12988: Civil Justice Reform

The Department has reviewed the regulations in light of sections 3(a) and 3(b)(2) of Executive Order 12988 to eliminate ambiguity, minimize litigation, establish clear legal standards, and reduce burden.

I. Executive Order 13175

The Department of State has determined that this rulemaking will not have tribal implications, will not impose substantial direct compliance costs on Indian tribal governments, and will not pre-empt tribal law. Accordingly, the requirements of Executive Order 13175 do not apply to this rulemaking.