



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 866

[Docket No. FDA-2011-N-0103]

Microbiology Devices; Classification of In Vitro Diagnostic Devices for Bacillus Species Detection

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule; reproposal of proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is re-proposing to classify in vitro diagnostic devices for Bacillus species (spp.) detection into class II (special controls) after considering, among other information, the recommendations of the Microbiology Devices Advisory Panel (the Panel). FDA is re-proposing to establish special controls in a draft special controls guideline that the Agency believes are necessary to provide a reasonable assurance of the safety and effectiveness of the devices. In addition, FDA is re-proposing to restrict use and distribution of the devices. FDA is publishing in this proposed rule the recommendations of the Panel regarding the classification of the devices.

DATES: Submit either electronic or written comments on the proposed rule by **[INSERT DATE 90 DAYS AFTER DATE OF PUBLICATION IN THE FEDERAL REGISTER]**.

ADDRESSES: You may submit comments as follows:

Electronic Submissions

Submit electronic comments in the following way:

- Federal eRulemaking Portal: <http://www.regulations.gov>. Follow the instructions for submitting comments. Comments submitted electronically, including attachments, to

<http://www.regulations.gov> will be posted to the docket unchanged. Because your comment will be made public, you are solely responsible for ensuring that your comment does not include any confidential information that you or a third party may not wish to be posted, such as medical information, your or anyone else's Social Security number, or confidential business information, such as a manufacturing process. Please note that if you include your name, contact information, or other information that identifies you in the body of your comments, that information will be posted on <http://www.regulations.gov>.

- If you want to submit a comment with confidential information that you do not wish to be made available to the public, submit the comment as a written/paper submission and in the manner detailed (see "Written/Paper Submissions" and "Instructions").

Written/Paper Submissions

Submit written/paper submissions as follows:

- Mail/Hand delivery/Courier (for written/paper submissions): Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.
- For written/paper comments submitted to the Division of Dockets Management, FDA will post your comment, as well as any attachments, except for information submitted, marked and identified, as confidential, if submitted as detailed in "Instructions."

Instructions: All submissions received must include the Docket No. FDA-2011-N-0103 for "Microbiology Devices; Classification of In Vitro Diagnostic Devices for Bacillus Species Detection." Received comments will be placed in the docket and, except for those submitted as

"Confidential Submissions," publicly viewable at <http://www.regulations.gov> or at the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday.

- Confidential Submissions--To submit a comment with confidential information that you do not wish to be made publicly available, submit your comments only as a written/paper submission. You should submit two copies total. One copy will include the information you claim to be confidential with a heading or cover note that states "THIS DOCUMENT CONTAINS CONFIDENTIAL INFORMATION." The Agency will review this copy, including the claimed confidential information, in its consideration of comments. The second copy, which will have the claimed confidential information redacted/blacked out, will be available for public viewing and posted on <http://www.regulations.gov>. Submit both copies to the Division of Dockets Management. If you do not wish your name and contact information to be made publicly available, you can provide this information on the cover sheet and not in the body of your comments and you must identify this information as "confidential." Any information marked as "confidential" will not be disclosed except in accordance with 21 CFR 10.20 and other applicable disclosure law. For more information about FDA's posting of comments to public dockets, see 80 FR 56469, September 18, 2015, or access the information at:

<http://www.fda.gov/regulatoryinformation/dockets/default.htm>.

Docket: For access to the docket to read background documents or the electronic and written/paper 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: Beena Puri, Center for Devices and Radiological Health, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 66, rm. 5553, Silver Spring, MD 20993-0002, 301-796-6202.

SUPPLEMENTARY INFORMATION:

I. Background

A. Regulatory Authorities

The Federal Food, Drug, and Cosmetic Act (the FD&C Act) (21 U.S.C. 301 et seq.), as amended, establishes a comprehensive system for the regulation of medical devices intended for human use. Section 513 of the FD&C Act (21 U.S.C. 360c) establishes three categories (classes) of devices, reflecting the regulatory controls needed to provide reasonable assurance of their safety and effectiveness. The three categories of devices are class I (general controls), class II (special controls), and class III (premarket approval).

Under section 513(d) of the FD&C Act, FDA refers to devices that were in commercial distribution before May 28, 1976 (the date of enactment of the Medical Device Amendments of 1976 (Pub. L. 94-295)), as "preamendments devices." FDA classifies these devices after it:

(1) Receives a recommendation from a device classification panel (an FDA advisory committee); (2) publishes the panel's recommendation for comment, along with a proposed regulation classifying the device; and (3) publishes a final regulation classifying the device. FDA has classified most preamendments devices under these procedures.

A person may market a preamendments device that has been classified into class III through premarket notification procedures, without submission of a premarket approval application (PMA), until FDA issues a final order under section 515(b) of the FD&C Act (21 U.S.C. 360e(b)) requiring premarket approval.

FDA refers to devices that were not in commercial distribution before May 28, 1976, as "postamendments devices." These devices are classified automatically by statute (section 513(f)(1) of the FD&C Act) into class III without any FDA rulemaking process. These devices remain in class III and require premarket approval, unless and until FDA classifies or reclassifies the device into class I or class II or FDA issues an order finding the device to be substantially equivalent in accordance with section 513(i) of the FD&C Act, to a predicate device that does not require premarket approval. The Agency determines whether new devices are substantially equivalent to predicate devices by means of premarket notification procedures in section 510(k) of the FD&C Act (21 U.S.C. 360(k)) and 21 CFR part 807.

Section 510(m) of the FD&C Act (21 U.S.C. 360(m)) provides that a class II device may be exempt from the premarket notification requirements under section 510(k) if the Agency determines that premarket notification is not necessary to provide reasonable assurance of the safety and effectiveness of the device.

Section 520(e) of the FD&C Act (21 U.S.C. 360j(e)) authorizes FDA to issue regulations imposing restrictions on the sale, distribution, or use of a device, if, because of its potentiality for harmful effect or the collateral measures necessary to its use, FDA determines that absent such restrictions, there cannot be a reasonable assurance of its safety and effectiveness. Certain provisions of the FD&C Act relate specifically to FDA's authority over restricted devices. For example, section 502(q) and (r) of the FD&C Act (21 U.S.C. 352(q) and (r)) provide that a restricted device distributed or offered for sale in any state shall be deemed to be misbranded if its advertising is false or misleading or fails to include certain information regarding the device, or it is sold, distributed, or used in violation of regulations prescribed under section 520(e) of the

FD&C Act, and section 704(a) of the FD&C Act (21 U.S.C. 374(a)) authorizes FDA to inspect certain records relating to restricted devices.

B. Regulatory History--Background of the Device

After the enactment of the Medical Device Amendments of 1976, FDA undertook to identify and classify all preamendments devices in accordance with section 513(b) of the FD&C Act. However, in vitro diagnostic devices for Bacillus spp. detection were not identified and classified in FDA's initial efforts. FDA subsequently identified several preamendments devices for Bacillus spp. detection, including Bacillus spp. antisera conjugated with a fluorescent dye (immunofluorescent reagents) used to presumptively identify bacillus-like organisms in clinical specimens, antigens used to identify antibodies to Bacillus anthracis (B. anthracis) (anti-toxin and anti-capsular) in serum, and bacteriophage used for differentiating B. anthracis from other Bacillus spp. based on susceptibility to lysis by the phage.

Consistent with the FD&C Act, FDA held a panel meeting on March 7, 2002, regarding the classification of the preamendments in vitro diagnostic devices for Bacillus spp. detection (Ref. 1). After the Panel meeting, FDA found three additional in vitro diagnostic devices for Bacillus spp. detection to be substantially equivalent to another device within that type. These three devices have the same intended use as their predicate devices, but make use of newer nucleic acid amplification technology. While they exhibit technological differences from the preamendments Bacillus spp. detection devices, FDA has determined that they are as safe and effective as, and do not raise different questions of safety and effectiveness than, their predicates. (See section 513(i) of the FD&C Act).

In the Federal Register of May 18, 2011 (76 FR 28688; 76 FR 28689), FDA proposed to classify these devices into class II, establish special controls in a draft special controls guidance

entitled "Class II Special Controls Guidance Document: In Vitro Diagnostic Devices for Bacillus spp. Detection," and limit the distribution of these devices to laboratories with experienced personnel who have training in principles and use of microbiological culture identification methods and infectious disease diagnostics and with appropriate biosafety equipment and containment. In the Federal Register of May 6, 2015 (80 FR 26059), FDA withdrew the previously issued draft special controls guidance entitled "Class II Special Controls Guidance Document: In Vitro Diagnostic Devices for Bacillus spp. Detection." This withdrawal was part of FDA's Transparency Initiative and was part of a withdrawal of a number of guidances that had not been finalized for several years.

II. Panel Recommendation

During a public meeting held on March 7, 2002, the Panel made the following recommendations regarding the classification of in vitro diagnostic devices for Bacillus spp. detection (Ref. 1).

A. Classification Recommendation

The Panel recommended that in vitro diagnostic devices for Bacillus spp. detection be classified into class II. The Panel believed that general and special controls would provide reasonable assurance of the safety and effectiveness of the devices.

The Panel recommended that the use of these devices be limited to prescription use, and also that distribution of the devices be limited to: (1) Persons with specific training or experience in the applicable testing methods and (2) facilities under the oversight of public health laboratories so that the laboratories could coordinate and communicate with state and local public health directors and so that performance of the devices in the laboratory might be systematically collated for interagency review (including FDA).

The Panel suggested: (1) That FDA partner with the Centers for Disease Control and Prevention, United States Army Medical Research Institute for Infectious Diseases (USAMRIID), and other appropriate Agencies involved in laboratory performance issues to develop practical ways to evaluate the performance of these devices; (2) that appropriate biosafety handling of the diagnostic specimens be followed by laboratories; and (3) that FDA develop testing guidelines to include recommendations on specimen selection, procedures, interpretation of results, and possibly public health notification.

B. Summary of Reasons and Data to Support the Recommendations

At the March 7, 2002, meeting, the Panel considered information from the literature presented by FDA (Refs. 2 to 7), information presented at the meeting by representatives from USAMRIID who shared the historical perspective on their institution's use of devices for the detection of B. anthracis and their personal experience using these devices, and the Panel's personal knowledge and experience.

Evidence presented to the Panel addressed how the preamendments devices of this type work and some of their limitations (Ref. 1). Bacteriophage tests are used for differentiating B. anthracis from other Bacillus spp. based on susceptibility to lysis by the phage. They have been shown to specifically lyse vegetative B. anthracis and not Bacillus cereus (B. cereus) strains, although the phage can fail to lyse rare strains of B. anthracis or lyse Bacillus strains other than B. anthracis. Bacillus spp. antisera tests conjugated with a fluorescent dye (immunofluorescent reagents) are used to microscopically visualize specific binding with cultured bacteria. Gram positive rods with capsules that fluoresce are presumptive evidence for identification of B. anthracis and must be confirmed with further testing. Antigen tests are used to identify antibodies to B. anthracis (anti-toxin and anti-capsular) in serum. They can be used

for confirmation of anthrax if the patient survives the disease, because early antibiotic treatment does not abrogate antibody expression. However, such serological testing is most useful for monitoring responses to anthrax vaccines and for epidemiological investigations.

III. Proposed Classification

FDA is proposing the following identification based on the Panel's discussion and recommendation, FDA's experience with these devices, and other available information. An in vitro diagnostic device for Bacillus spp. detection is a prescription device used to detect and differentiate among Bacillus spp. and presumptively identify B. anthracis and other Bacillus spp. from cultured isolates or clinical specimens as an aid in the diagnosis of anthrax and other diseases caused by Bacillus spp. This device may consist of Bacillus spp. antisera conjugated with a fluorescent dye (immunofluorescent reagents) used to presumptively identify bacillus-like organisms in clinical specimens; bacteriophage used for differentiating B. anthracis from other Bacillus spp. based on susceptibility to lysis by the phage; or antigens used to identify antibodies to B. anthracis (anti-toxin and anti-capsular) in serum. Bacillus infections include anthrax (cutaneous, inhalational, or gastrointestinal) caused by B. anthracis, and gastrointestinal disease and non-gastrointestinal infections caused by B. cereus.

FDA is proposing to classify these devices into class II because general controls are insufficient to provide reasonable assurance of the safety and effectiveness of the devices, and there is sufficient information to establish special controls to provide such assurance (see section V). For these devices, FDA believes that premarket notification is necessary to provide reasonable assurance of safety and effectiveness and, therefore, FDA does not intend to exempt the devices from premarket notification requirements.

IV. Risks to Health

Based on the Panel's discussion and recommendations, FDA's experience with these devices, and other available information, we believe the risks to health associated with the use of the device type are those discussed below. No new risks or significant changes in risks relating to this device type have been identified since the Panel meeting.

Although there have been no reports to date, FDA believes that this type of device presents risks associated with false negative and false positive test results, which could result from device performance failures or errors in interpretation. A false positive result may lead to a patient undergoing unnecessary or ineffective treatment, and also could result in inaccurate epidemiological information on the presence of anthrax disease being publicized in a community, potentially leading to unnecessary prophylaxis and management of others. A false negative result may lead to delayed recognition by the physician of the presence or progression of disease and also could result in a failure to promptly recognize, control, and prevent additional infections. A false negative result could potentially delay diagnosis and treatment of infection caused by B. anthracis or other Bacillus spp.

In addition, while there have been few reports to date, there may be risks to laboratory workers from handling cultures and control materials. Improper handling of cultures and control materials may expose laboratory workers to serious health problems associated with infection caused by B. anthracis or other Bacillus spp. Because handling the quality control organisms and those potentially present in the specimen may pose a risk to laboratory workers, FDA is proposing to restrict distribution of these products to laboratories that follow public health guidelines that address appropriate biosafety conditions, interpretation of test results, and coordination of findings with public health authorities.

V. Special Controls

Based on the Panel's discussion and recommendations, FDA's experience with these devices, and other available information, FDA is proposing to establish the special controls set forth in the draft guideline document entitled "Class II Special Controls Guideline: In Vitro Diagnostic Devices for Bacillus spp. Detection" (Ref. 8). FDA believes that these special controls, in combination with general controls, are necessary to provide a reasonable assurance of safety and effectiveness of the devices. As discussed further in section XI, for currently marketed devices, FDA does not intend to enforce compliance with the submission requirement for the special controls set forth in sections VI, VII, and IX of the special controls guideline. Manufacturers of such devices must comply with the underlying requirements for those special controls as well as the labeling special controls set forth in section VIII of the guideline.

The class II special controls guideline, which sets forth criteria that are supplemental to other applicable requirements, addresses: (1) Specific information relating to the devices' intended use, components, testing procedures, specimen storage/shipping conditions, and interpretation/reporting that must be submitted to FDA; (2) detailed descriptive information submitted to FDA regarding the studies required to demonstrate appropriate performance and control against assays that may otherwise fail to perform to acceptable standards; (3) specific labeling requirements; and (4) certain information that must be submitted for in vitro diagnostic devices for Bacillus spp. detection that use nucleic acid amplification.

First, the submission of specific information to FDA related to the devices' intended use, components, testing procedures, specimen storage/shipping conditions, and interpretation/reporting would help mitigate the risks of false positive and false negatives as well as the biosafety risks of such devices because such information would help FDA to assess the safety and effectiveness of the devices. Second, detailed descriptive information regarding the

studies required to demonstrate performance and control would mitigate the risk of false negatives and false positives by helping to ensure that the devices performs to acceptable standards. Third, specific labeling requirements would mitigate the risk of false positives, false negatives, and biosafety risks associated with the devices by helping to ensure that users understand the appropriate uses and limitations of the devices as well as the biosafety risks associated with the devices. Lastly, certain information that must be submitted to FDA for in vitro diagnostic devices for Bacillus spp. detection that use nucleic acid amplification would mitigate the risk of false positives and false negatives, as such information would allow FDA to assess the safety and effectiveness of the devices and the regulatory controls necessary to address those issues as well as to ensure the devices performs to acceptable standards.

Manufacturers of diagnostic devices for Bacillus spp. detection would need either to:

- (1) Comply with the particular mitigation measures set forth in the special controls guideline or
- (2) use alternative mitigation measures, but demonstrate to the Agency's satisfaction that alternative mitigation measures identified by the firm would provide at least an equivalent assurance of safety and effectiveness.

Table 1.--Identified Risks and Mitigation Measures

Identified Risks	Mitigation Measures
A false negative test result may lead to delay of therapy and progression of disease and failure to promptly recognize, control, and prevent disease in the community.	The FDA document entitled "Class II Special Controls Guideline: In Vitro Diagnostic Devices for <u>Bacillus</u> spp. Detection," which addresses this risk through: Specific device description requirements, performance studies, labeling, and specific requirements for devices that use nucleic acid amplification.
A false positive test result may lead to unnecessary or ineffective treatment and incorrect epidemiological information being publicized, potentially leading to unnecessary prophylaxis and management of others.	The FDA document entitled "Class II Special Controls Guideline: In Vitro Diagnostic Devices for <u>Bacillus</u> spp. Detection," which addresses this risk through: Specific device description requirements, performance studies, labeling, and specific requirements for devices that use nucleic acid amplification.
Biosafety risks to laboratory workers handling test specimens and control materials	The FDA document entitled "Class II Special Controls Guideline: In Vitro Diagnostic Devices for <u>Bacillus</u> spp. Detection," which addresses this risk through: Specific device description requirements and labeling.

VI. Restrictions on Distribution and Use

FDA also believes that restrictions on the distribution and use of the devices are necessary to provide a reasonable assurance of safety and effectiveness. FDA proposes to restrict distribution of the devices to laboratories that follow public health guidelines that address the appropriate biosafety conditions, interpretation of test results, and coordination of findings with public health authorities. As noted, the Panel was concerned that these devices be used by personnel sufficiently skilled to maximize device performance and to appropriately interpret and make use of test results. FDA believes that this proposed distribution restriction is necessary to provide a reasonable assurance of safety and effectiveness of these devices, and that it would be consistent with the intent of the Panel in its discussion of limitations on the distribution of the devices and on monitoring of test results.

Further, FDA proposes to restrict use of these devices to be a prescription device in accordance with the terms set forth in proposed 21 CFR 866.3045(d).

VII. Electronic Access

Persons interested in obtaining a copy of the draft guideline may do so by using the Internet. A search capability for all Center for Devices and Radiological Health guidelines and guidance documents is available at <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/default.htm>. The draft guideline is also available at <http://www.regulations.gov>. Persons unable to download an electronic copy of "Class II Special Controls Guideline: In Vitro Diagnostic Devices for Bacillus spp. Detection," may send an email request to CDRH-Guidance@fda.hhs.gov to receive an electronic copy of the document. Please use the document number 1400038 to identify the guideline you are requesting.

VIII. Environmental Impact

The Agency has determined that under 21 CFR 25.34(b) and (f), this proposed 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.

IX. Paperwork Reduction Act of 1995

This proposed rule refers to previously approved collections of information found in FDA regulations. These collections of information are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (the PRA) (44 U.S.C. 3501-3520). The collections of information in 21 CFR part 807, subpart E, have been approved under OMB control number 0910-0120 and the collections of information in 21 CFR parts 801 and 809 have been approved under OMB control number 0910-0485.

The labeling referenced in sections VI(A), VIII(A), and VIII(C) of the draft special controls guideline do not constitute a "collection of information" under the PRA because the labeling is a "public disclosure of information originally supplied by the Federal government to the recipient for the purpose of disclosure to the public" (5 CFR 1320.3(c)(2)).

X. Clarifications to Special Controls Guidelines

The draft special controls guideline reflects changes the Agency has made since the initial proposed rule to clarify its position on the binding nature of special controls. The changes include referring to the document as a "guideline," as that term is used in section 513(a) of the FD&C Act (21 U.S.C. 360c(a)), which the Agency has developed and disseminated to provide a reasonable assurance of safety and effectiveness for class II devices, and not a "guidance," as that term is used in 21 CFR 10.115. The draft guideline clarifies that firms submitting 510(k)s would need either to: (1) Comply with the particular mitigation measures set forth in the special controls guideline or (2) use alternative mitigation measures, but demonstrate to the Agency's satisfaction that those alternative measures identified by the firm will provide at least an equivalent assurance of safety and effectiveness. Finally, the draft guideline uses mandatory language to emphasize that firms must comply with special controls to legally market their class II devices. These revisions do not represent a change in FDA's position about the binding effect of special controls, but rather are intended to address any possible confusion or misunderstanding.

XI. Implementation Strategy

FDA proposes the implementation strategy set forth below for these devices if a final rule becomes effective.

- Devices that have not been legally marketed prior to the date of publication of any final rule, or devices that have been legally marketed, but are required to submit a new 510(k) under 21 CFR 807.81(a)(3) because the device is about to be significantly changed or modified: Manufacturers must obtain 510(k) clearance and comply with special controls before marketing the new or changed device.
- Devices that have been legally marketed prior to the date of publication of any final rule, and devices for which 510(k) submissions have been submitted before the date of publication of any final rule: FDA does not intend to enforce compliance with the submission requirement for the special controls set forth in sections VI, VII, and IX of the special controls guideline. Manufacturers of such devices must comply with the underlying requirements for those special controls as well as the labeling special controls set forth in section VIII of the guideline.

XII. Analysis of Impacts

A. Economic Analysis of Impacts

FDA has examined the impacts of this proposed rule under Executive Order 12866, Executive Order 13563, the Regulatory Flexibility Act (5 U.S.C. 601-612), and the Unfunded Mandates Reform Act of 1995 (Pub. L. 104-4). Executive Orders 12866 and 13563 direct Agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). The Agency believes that this proposed rule is not a significant regulatory action under 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 of the minor impact expected from this proposed action, the Agency proposes to certify that the proposed rule, when finalized, will 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 \$144 million, using the most current (2014) Implicit Price Deflator for the Gross National Product. FDA does not expect this proposed rule, when finalized, to result in any 1-year expenditure that would meet or exceed this amount.

B. Summary of Costs and Benefits

The proposed rule would require the adoption of practices most of which manufacturers of currently marketed in vitro diagnostic devices for Bacillus spp. detection already follow. The costs of the proposed rule, when finalized, will be due to manufacturers ensuring that product labeling is consistent with the special controls guideline document as well as conducting likely periodic quality control testing to assure that marketed devices continue to operate at appropriate levels of safety and effectiveness. The costs associated with ensuring labeling is consistent with the guideline are expected to be minor. The required labeling is similar to the cleared indications for use of currently cleared devices and so little change from current labeling is expected. However, because of this regulatory action, it is possible that these additional activities will

result in minor cost increases. We have estimated that the proposed rule, if finalized, could result in, at most, annualized costs of approximately \$2,300 (3 percent) or \$2,500 (7 percent).

There are unlikely to be any direct public health benefits from the proposed rule, if finalized, because the rule would require the adoption of practices most of which manufacturers of currently marketed devices already follow and would not change the expected use of the diagnostic product. However, we estimate the proposed regulation, when final, will result in quantifiable benefits of reducing the number of inquiries and incomplete 510(k) submissions from manufacturers to FDA (thereby reducing FDA resources needed to answer those inquiries and review those submissions) to be between approximately \$1,400 and \$3,400 per year. We believe that the unquantified benefits of the draft special controls guideline, which would help to ensure the quality of these devices, maintain their predictive value, and avoid potential future laboratory errors, cannot be estimated, but represent real benefits to the public health.

The full discussion of economic impacts is available in Docket No. FDA-2011-N-0103 and at <http://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/EconomicAnalyses/default.htm> (Ref. 9).

XIII. References

The following references are on display in the Division of Dockets Management (see ADDRESSES) and are available for viewing by interested persons between 9 a.m. and 4 p.m., Monday through Friday; they are also available electronically at <http://www.regulations.gov>. FDA has verified the Web site addresses, as of the date this document publishes in the Federal Register, but Web sites are subject to change over time.

1. Transcript of the FDA Microbiology Devices Panel meeting, March 7, 2002, available at
<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfAdvisory/details.cfm?mtg=348>.
2. Abshire, T. G., J. E. Brown, and J. W. Ezzell, "Validation of the Use of Gamma Phage for Identifying Bacillus anthracis," 102nd American Society for Microbiology Annual Meeting (poster #C122), 2001.
3. Abshire, T. G., et al., "Production and Validation of the Use of Gamma Phage for the Identification of Bacillus anthracis," Journal of Clinical Microbiology, vol. 43(9), pp. 4780-8, 2005, available at <http://www.ncbi.nlm.nih.gov/pubmed/16145141>.
4. Brown, E. R. and W. B. Cherry, "Specific Identification of Bacillus anthracis by Means of a Variant Bacteriophage," Journal of Infectious Disease, vol. 96, p. 34, 1955, available at <http://jid.oxfordjournals.org/content/96/1/34.long>.
5. Brown, E. R. et al., "Differential Diagnosis of Bacillus cereus, Bacillus anthracis, and Bacillus cereus var. mycoides," Journal of Bacteriology, vol. 75, p. 499, 1958, available at
<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC290100/pdf/jbacter00512-0024.pdf>.
6. Buck C. A., R .L. Anacker, F. S. Newman, et al., "Phage Isolated from Lysogenic Bacillus anthracis," Journal of Bacteriology, vol. 85, p. 423, 1963, available at
<http://jb.asm.org/content/85/6/1423.full.pdf+html?sid=c14df35d-1d7b-4cac-b55b-2097931a4623>.
7. Parry, J. M., P. C. B. Turnbull, and J. R. Gibson, A Colour Atlas of Bacillus Species, Wolfe Medical Publications Ltd., London, 1983.

8. Draft Guideline for Industry and Food and Drug Administration Staff, "Class II Special Controls Guideline: In Vitro Diagnostic Devices for Bacillus spp. Detection," issued [INSERT DISPLAY DATE OF THIS DOCUMENT], available at <http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM470760.pdf>.

9. "Preliminary Regulatory Impact Analysis, Initial Regulatory Flexibility Analysis, and Unfunded Mandates Reform Act Analysis for Microbiology Devices; Classification of In Vitro Diagnostic Device for Bacillus Species Detection," available at <http://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/EconomicAnalyses/default.htm>.

List of Subjects in 21 CFR Part 866

Biologics, Laboratories, Medical devices.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, it is proposed that 21 CFR part 866 is amended as follows:

PART 866--IMMUNOLOGY AND MICROBIOLOGY DEVICES

1. The authority citation for 21 CFR part 866 continues to read as follows:

Authority: 21 U.S.C. 351, 360, 360c, 360e, 360j, 371.

2. Section 866.3045 is added to subpart D to read as follows:

§ 866.3045 In vitro diagnostic device for "Bacillus" spp. detection.

(a) Identification. An in vitro diagnostic device for Bacillus species (spp.) detection is a prescription device used to detect and differentiate among Bacillus spp. and presumptively identify B. anthracis and other Bacillus spp. from cultured isolates or clinical specimens as an aid

in the diagnosis of anthrax and other diseases caused by Bacillus spp. This device may consist of Bacillus spp. antisera conjugated with a fluorescent dye (immunofluorescent reagents) used to presumptively identify bacillus-like organisms in clinical specimens; bacteriophage used for differentiating B. anthracis from other Bacillus spp. based on susceptibility to lysis by the phage; or antigens used to identify antibodies to B. anthracis (anti-toxin and anti-capsular) in serum. Bacillus infections include anthrax (cutaneous, inhalational, or gastrointestinal) caused by B. anthracis, and gastrointestinal disease and non-gastrointestinal infections caused by B. cereus.

(b) Classification. Class II (special controls). The special controls are set forth in FDA's guideline document entitled "Class II Special Controls Guideline: In Vitro Diagnostic Devices for Bacillus spp. Detection; Guideline for Industry and Food and Drug Administration Staff." See § 866.1(e) for information on obtaining this document.

(c) The distribution of these devices is limited to laboratories that follow public health guidelines that address appropriate biosafety conditions, interpretation of test results, and coordination of findings with public health authorities.

(d) The use of this device is restricted to prescription use and must comply with the following:

(1) The device must be in the possession of:

(i)(A) A person, or his agents or employees, regularly and lawfully engaged in the manufacture, transportation, storage, or wholesale or retail distribution of such device; or

(B) A practitioner, such as a physician, licensed by law to use or order the use of such device; and

(ii) The device must be sold only to or on the prescription or other order of such practitioner for use in the course of his professional practice.

(2) The label of the device shall bear the statement "Caution: Federal law restricts this device to sale by or on the order of a _____", the blank to be filled with the word "physician" or with the descriptive designation of any other practitioner licensed by the law of the State in which he practices to use or order the use of the device.

(3) Any labeling, as defined in section 201(m) of the FD&C Act, whether or not it is on or within a package from which the device is to be dispensed, distributed by, or on behalf of the manufacturer, packer, or distributor of the device, that furnishes or purports to furnish information for use of the device contains adequate information for such use, including indications, effects, routes, methods, and frequency and duration of administration and any relevant hazards, contraindications, side effects, and precautions, under which practitioners licensed by law to employ the device can use the device safely and for the purposes for which it is intended, including all purposes for which it is advertised or represented. This information will not be required on so-called reminder-piece labeling which calls attention to the name of the device but does not include indications or other use information.

(4) All labeling, except labels and cartons, bearing information for use of the device also bears the date of the issuance or the date of the latest revision of such labeling.

Dated: November 10, 2015.

Leslie Kux,

Associate Commissioner for Policy.

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