

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

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

Docket No. FDA-2011-N-0103

Preliminary Regulatory Impact Analysis
Initial Regulatory Flexibility Analysis
Unfunded Mandates Reform Act Analysis

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Preface: Summary of the Proposed Rule

The Food and Drug Administration (FDA) is proposing to classify in vitro diagnostic devices for *Bacillus* species (spp.) detection into class II (special controls), in accordance with the recommendations of the Microbiology Devices Advisory Panel (the Panel). FDA is also issuing a draft special controls guideline that the Agency believes is necessary to provide a reasonable assurance of the safety and effectiveness of the device. In addition, when final, the rule will establish restrictions on use and distribution of this device.

I. Introduction

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

The Regulatory Flexibility Act requires agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities. Because of the minor impact expected from this proposed classification, 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 \$141 million, using the most current (2013) Implicit Price Deflator for the Gross Domestic Product. FDA does not expect this proposed rule to result in any 1-year expenditure that will meet or exceed this amount.

II. Summary of Costs and Benefits

The proposed rule would require the adoption of practices most of which manufacturers of currently marketed devices 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 likely periodic quality control testing to ensure that marketed devices maintain 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 conditions is expected. However, because of this regulatory classification, it is possible that these additional activities will result in minor cost increases. We have estimated that the 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 of 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 \$1,376 and \$3,441 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.

III. Objective

The objective of the regulation is to provide a reasonable assurance of the safety and effectiveness of in vitro diagnostic devices for the identification of potential Bacillus (Bacillus spp.) infections.

IV. Baseline

Since the 1950s, diagnostic tests have been used to detect Bacillus spp., differentiate between species, and identify B. anthracis from culture isolates or clinical specimens. Over the 10-year period from 1999 to 2009, there have been approximately 8,000 such tests (using the estimated annual testing rate), the vast majority of which were for the purposes of proficiency testing and training. No accidents have been reported associated with these tests.

There are currently five diagnostic devices cleared from different manufacturers, as well as devices developed by Centers for Disease Control and Prevention (CDC) and Department of Defense. The CDC devices have been distributed to approximately 114 laboratories that belong to the national Laboratory Response Network. Devices are able to test between 10 and 100 samples depending on the testing capability of the different devices. The alternative to using in vitro diagnostic devices to identify potential exposure to B. anthracis is to use blood, fluid, and tissue specimens to grow cultures that may be used to identify the bacillus. This method is more time-consuming and presents risks that the disease (if present) will progress and be more difficult to treat when identified. It also means increased patient anxiety while the culture is growing, whether the patient has been exposed or not. A patient that may have contracted inhalational anthrax would be expected to have high levels of anxiety while awaiting diagnosis. The diagnostic devices

offer significant public health benefits by providing rapid diagnosis that can both save lives by identifying patients with anthrax and rapidly beginning treatment as well as avoiding unnecessary prophylactic treatments for patients that are found to not have the bacillus.

Currently most marketed diagnostic devices have extremely high predictive values. Sensitivities of these devices (proportion of positive patients correctly identified by the test) have been tested to be over 99 percent and specificities (proportion of negative patients correctly identified by the test) approach 100 percent.

After the 2001 incident of inhalational anthrax exposures, there was an increased public awareness of the risk of contracting anthrax due to the media publicity that surrounded the event. Fourteen manufacturers reacted to this increased public attention by submitting inquiries to FDA about obtaining marketing clearance for additional products that would diagnose the presence of the bacillus. Two of these manufacturers subsequently received clearance for their devices through the Premarket Notification (510(k)) process and one manufacturer submitted an Investigational Device Exemption (IDE). The remaining manufacturers expressed interest but decided not to submit 510(k) notifications.

Another inhalational anthrax exposure event would likely lead to an increased level of public attention and concern (such as in 2001) and would likely cause similar responses from potential manufacturers. In the absence of this rule, there will likely continue to be ambiguity as to the specific testing criteria necessary for the device to be cleared for marketing. In addition, FDA resources will be spent responding to these inquiries for products that will never be marketed.

V. The Regulation

We are proposing classifying anthrax diagnostic devices into class II, designating special controls, and restricting use and distribution of the device. The draft special controls guideline provides for the submission of certain performance data and quality control information, as well as labeling for the device. This guideline document, when final, will be unlikely to affect the number of laboratory tests for Bacillus spp. or the number of tests used for training purposes. Generally, the guideline would require the adoption of measures most of which are already being practiced by manufacturers of currently marketed devices. The guideline, when finalized, will also not likely result in any procedural changes in how laboratories handle the diagnostic devices because we have been interacting with manufacturers individually to ensure safety and effectiveness and the guideline document reflects the practices discussed with and adopted by laboratories. The proposed rule, when finalized, will help to ensure that information provided to manufacturers and users of these diagnostic devices is consistent and appropriate, and will restrict distribution to laboratories that follow public health guidelines that address appropriate biosafety condition, interpretation of tests results and coordination of findings with public health authorities.

VI. Impact of the Regulation

If the regulation is implemented, potential marketers of these devices would clearly know what criteria and what evidence would be needed to ensure clearance and legal marketing of their devices. In addition, laboratory personnel would have assurance that they are handling the devices appropriately, thus both ensuring that the predictive value of the devices are maximized and any potential risk of exposure to pathogens due to careless handling of the devices remain minimized.

That being said, we do not expect any changes in the efficacy or amount of use of the device as a result from the regulation. The current predictive values of the devices are already extremely high. Of the five products currently cleared, there have been no reports of false positive (specificity of 100 percent) and few reports of false negatives (estimated sensitivity of 99.6 percent combining all products) since the devices received clearance. Therefore, we do not expect any change in either use of the devices by laboratories or in the predictive value of the devices in patients. The proposed rule, when finalized, will, however, establish special controls to help to ensure that the devices provide accurate and timely diagnosis and that proper laboratory procedures are maintained to provide a reasonable assurance of safety and effectiveness.

VII. Costs

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 likely periodic quality control testing to ensure that marketed devices maintain 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. Nevertheless, we have estimated that manufacturers may incur minor revisions to their labels in response to the new guideline after regulatory staff review and compare current labeling language and design to the language and design mitigation measures (including photographs or diagrams) in the guideline document. To account for these reviews and any possible labeling revisions, we have estimated that typical label changes for typical medical devices or diagnostic products would cost manufacturers approximately \$2,200 per label change per brand. This estimate is based on market driven label revisions and was derived from estimates for a variety of devices similar to devices (Cost Analysis of the Labeling and Related Testing Requirements for Medical Glove Manufacturers, Eastern Research Group (ERG), 2002) and account for only simple language and design alterations. We have further estimated that changes of this sort typically occur about every 5 years in response to market changes and improvements to the specific product. The manufacturers of each of the 4 currently marketed devices are likely to review and perhaps revise labels for a total cost of \$8,800. Over an expected 5-year evaluation period (based on a typical labeling cycle), the annualized cost of reviewing and revising labels is only \$1,900 (3-percent annual discount rate) or \$2,100 (7-percent annual discount rate).

In addition, the draft guideline document, if finalized, will address quality control tests that manufacturers must perform to ensure the safety and effectiveness of the devices. While these tests are currently used to develop marketed products, it is possible that the frequency of testing to ensure continued quality may increase as a result of the rule. We have estimated that additional quality control testing may require expenditures of as much as \$100 per product per year for each brand. This cost is based on a sampling of typical laboratory control tests (including ELISHA, Lowry, and other American Society for Testing of Materials (ASTM) recommended tests) for devices (ERG, 2002). Therefore, for the duration of a 5-year evaluation period, we expect the industry may incur additional quality control testing costs of about \$400 per year.

The proposed rule would require the adoption of practices most of which manufacturers of currently marketed devices already follow. However, because of this proposed rule, it is possible that these additional activities would result in minor cost increases. We have estimated that the rule, if finalized, could result in, at most, annualized costs of approximately \$2,300 (3 percent) or \$2,500 (7 percent).

VIII. Benefits

There are unlikely to be any direct public health benefits of 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, the regulation is designed to provide a reasonable assurance of safety and effectiveness of this important diagnostic tool. The Bacillus spp. device provides important public health benefits through rapid diagnosis and thus, rapid treatment of a fatal disease, or rapid identification that treatment is not necessary. The absence of this diagnostic device, or even a decrease in the performance of the device, would increase the negative outcomes of any future anthrax event, including increases in potential mortalities. The proposed regulation, when finalized, will provide additional assurance that the current level of public health protection is maintained.

In addition, it is possible that any slight label revisions or standardization of information in the labeling, as well as an increased emphasis on laboratory training, may decrease the likelihood of potential mishandling of either the diagnostic devices or the test medium. There is currently no way to quantify this effect because there has been no reported exposure or risk associated with these diagnostic tests or the test medium in this country. We acknowledge that it is possible that mishandling could occur in the future and it is possible that clear, consistent instructions may avoid some potential future mishandling, but cannot quantify any benefit based on this eventuality.

However, the response of potential marketers of Bacillus spp. devices to the publicity that surrounded the 2001 anthrax event indicates that a potential benefit could be derived from clearly articulating the tests needed to provide sufficient data to provide a reasonable assurance of safety and effectiveness of these products. By having

consistent and easily available criteria, potential marketers will easily be able to ascertain whether or not to pursue market clearance. The availability of this information is expected to result in better, and perhaps fewer, potential marketing applications that may arise in response to future incidents of public inhalation anthrax exposure. Of course we hope that future events do not occur; however, there is a low level of probability that an incident could occur in the future. We have estimated the annual probability of a public inhalational anthrax incident to be approximately between 2 percent and 5 percent based on historical occurrences. We received 14 inquiries in regards to obtaining clearances which have resulted in 3 applications and 2 clearances. Using the success rate of 14 percent (2 successes from 14 inquiries), we expect a reduction of approximately 0.24 to 0.6 of unsuccessful inquiries or applications each year. (Twelve unsuccessful inquiries or applications multiplied by the annual probability of an incident). The estimated effort to potential marketers of contacting FDA, obtaining advice concerning the clearance process, and preliminarily preparing a marketing application is estimated to take approximately 5 days of review, market research, and internal decisionmaking. Labor hours are valued using the mean hourly wage for Management Occupations (occupation code 11-0000) in Medical and Diagnostic Laboratories (NCAIS code 621500) as reported by the Bureau of Labor Statistics 2013 Employment Occupational Statistics (BLS 2013). After adjusting for benefits and overhead (estimated at twice the real wage), the mean hourly wage is \$112. A week of FTE (full-time employee) time would thus have an average cost to manufacturers of about \$4,480. By avoiding unnecessary (and ultimately unsuccessful) inquiries for potential marketing applications, we expect the rule to result in savings of between \$1,075 and \$2,688 per year (\$4,480 multiplied by 0.24 and 0.6 avoided inquiries each year).

In addition, FDA resources will not be spent responding to inquiries or reviewing unsuccessful applications that would not be submitted with the necessary information, which would be clearly set forth in the rule. The average FDA FTE is valued at approximately \$295,000 (FY 2014), including salary, benefits, overhead, and support. Responding to inquiries concerning a potential application may consume a few hours of resources per inquiry while reviewing an application may consume as much as 2 weeks of review time. On average, we expect each avoided inquiry or application to save approximately 8 hours of FDA resources. Thus, with the clear information available as a result of the rule, FDA is expected to save between \$301 and \$753 per year (\$295,000 divided by 235 days times 0.24 and 0.6 annual inquiries avoided).

Thus, we estimate the proposed regulation, when final, will result in quantifiable benefits of avoiding unnecessary inquiries and potential applications to be between \$1,376 and \$3,441 per year. We believe that the unquantified benefits of providing an additional level of quality assurance, maintaining the predictive value of the marketed devices, and avoiding any potential future laboratory errors cannot be estimated, but represent real benefits to the public health.

IX. Alternatives to the Rule

We identified four plausible alternatives to the rule.

1. Continue to regulate as an unclassified device. This alternative would not provide an assurance of safety and effectiveness and would continue the current level of inconsistent information for potential new marketers.

2. Regulate this diagnostic test as a class I device. Because general controls were not sufficient to provide reasonable assurance of the safety and effectiveness of the device and sufficient information was available to develop special controls for this device, this alternative, which would require general controls only, was not considered sufficient for the potential risks of this device.

3. Regulate this diagnostic test as a class III device. Premarket approval and clinical data collection are not appropriate for the potential risks of this device, which are more appropriately dealt with using the special controls because sufficient information exists to determine that special controls would provide reasonable assurance of its safety and effectiveness. Classifying the test as class III would increase the cost of marketing the devices without an increase in assurances of safety and effectiveness.

4. Regulate this diagnostic test as a class II device with alternative special controls. The guideline document is sufficient to provide assurances of safety and effectiveness. Other potential special controls did not provide the necessary assurances of safety and effectiveness and were deemed to not be cost-effective.

X. Small Entity Effects

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 costs to manufacturing entities attributable to the rule, the Agency believes the proposed rule, if finalized, will not have a significant economic impact on a substantial number of small manufacturing entities. In addition, the rule will not affect testing laboratories because we do not expect any change in current use of the diagnostic device.

There are currently five cleared diagnostic devices for the identification of Bacillus spp. marketed by five companies. These companies are classified in the In Vitro Diagnostic Substance Manufacturing Industry (NAICS 325413) by the Census of Manufacturers. This industry is typified by small entities. For this industry, the Small Business Administration classifies any establishment with 500 or fewer employees as small. The typical establishment in this industry employs only about 120 employees, so virtually every company is small. Value of shipments for this industry is approximately \$50,000,000 per establishment. The expected annualized cost per affected establishment (\$800) represents less than 0.002 percent of annual shipments.

Testing Laboratories (NAICS 541380) are considered small by the Small Business Administration if they generate \$12,000,000 or less in annual revenue. There is no change in activity expected by this industry from the rule, so we do not expect any impact on laboratories.

XI. References

Bureau of Labor Statistics. 2013. "Employment Occupational Statistics". March 12, 2015.

Eastern Research Group. "Labeling and Related Testing Costs for Medical Glove Manufacturers". April 17, 2002.