DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Microbiology Devices; Reclassification of Nucleic Acid-Based Systems for *Mycobacterium tuberculosis* complex

Docket No. FDA-2012-N-0159

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

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I. Introduction and Summary

A. Introduction

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 (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 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 reclassification of this device from class III to class II will relieve manufacturers of the device of the cost of complying with the premarket approval requirements of section 515 of the FD&C Act (21 U.S.C. 360e), and may permit small potential competitors to enter the marketplace by lowering their costs, the agency certifies that the final rule 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 $136 million, using the most current (2010) 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. Summary

Our estimate of benefits annualized over 20 years is $9.4 million at a 3 percent discount rate and $7.4 million at a 7 percent discount rate. The change in pre- and post-marketing requirements between a 510(k) and a PMA lead to benefits in the form of reduced submission costs, review-related activities, and inspections. Another unquantifiable benefit from the rule is that a decrease in entry could lead to further product innovation. FDA is unable to quantify the costs that could arise if there is a change in risk which could lead to adverse events, recalls, warning letters, or unlisted letters.

II. Preliminary Regulatory Impact Analysis

A. Need for Regulation

There are currently two pre-market approvals (PMAs) for nucleic acid-based in vitro diagnostic devices for the detection of *Mycobacterium tuberculosis* complex, which is the only product affected by this rule (product code MWA). The two PMA approvals

occurred in 1995 and 1996, and since then FDA's Center for Devices and Radiological Health (CDRH) has not received any new original PMA submissions for devices of this intended use. The total sales volume for the affected firms, which includes other products not affected by this rule, is $626 million. We estimate that the average sale per product is between $3.3 million and $20.1 million. In addition to the PMA holders, there are six other firms which market seven products outside of the United States, and which are likely to seek FDA clearance if this rule is finalized. The estimated average sale per product for these manufacturers ranges between $7.0 million and at least $48.3 million.

In the period 1996 to 2011, CDRH has received a total of 26 PMA supplements—most of which are via normal 180 day track. Overall, the supplements submitted during the period 1995-2011 included changes to labeling (31 percent), location (23 percent) and processing (46 percent). In the period 2005-2010, CDRH approved an average of two supplements per year—one of the supplements was usually related to processing changes, while the other was for changes to location. This trend is different from the period 1996-2004, during which most of the PMA supplements were related to processing and labeling changes. On average, the firms in this product code were inspected at least once a year. In the last five years, inspections resulted in one warning letter and one untitled letter.

The objective of this proposed rule is to reclassify nucleic acid-based in vitro diagnostic devices for the detection of *M. tuberculosis* complex from class II (pre-market approval or PMA) to class II (special controls). A panel of experts expressed the opinion that sufficient data and information exist such that the risks of false positive and false negative results can be mitigated with special controls guidance. Furthermore, discussions at a public workshop, *Advancing the Development of Diagnostic Tests and Biomarkers for Tuberculosis* (June 7-8, 2010), suggested that the current regulatory requirements to submit a PMA present a barrier to potential improvements in market efficiency for this product. For instance, the regulatory requirements may pose a barrier to entry which could lead to the advancement of *M. Tuberculosis* diagnostics.. This rule addresses this potential failure by proposing to reclassify nucleic acid-based in vitro diagnostic devices for the detection of *M. tuberculosis* complex from class III into class II (special controls).

FDA has concluded that the proposed special control guidance provides reasonable assurance of the device's safety and effectiveness such that the risks to the public health are not altered. Declassification of MWA products would lower the cost of market entry, which could increase the supply and lower the costs of the marketed products. In addition to lowering market entry barriers, there could be potential savings from pre- and post-marketing related requirements.

B. Benefits and Costs

1. Number of Affected Entities

Table 1 below presents the number of 510(k) submissions that FDA anticipates when this rule is finalized. The low cost to entry will attract existing manufacturers who market the product outside of the United as well as manufacturers of new innovative devices in the detection of *M. tubercolosis* complex, e.g. multiplexed devices that simultaneously detect multiple organisms in the same specimen. Moreover, existing PMA holders will have the incentive to seek 510(k) clearance to reduce costs associated with PMA post-marketing requirements. FDA assumes that existing PMA holders and manufacturers who market their product outside of the United States will submit a 510(k) in the first year. FDA anticipates the receipt of 1 new 510(k) submission per year after the first year. Although the timing cannot be determined, given the low prevalence of pulmonary tuberculosis in the United States, FDA anticipates that one of every four new submissions will be from a foreign applicant. While submitting a 510(k) is less burdensome than submitting a PMA supplement, the threshold for submitting modifications to a 510(k) is higher than for modifications to a PMA. Thus, fewer changes could trigger the need for a submission to the Agency. Based in past PMA supplement submissions, we estimate that four 510(k) submissions will come from existing 510(k) applicants.

Table 1. - Number of 510(k) Submissions by Type of Applicant

Type of Applicant	Year 1	Post Year 1
Existing PMA Holders	2	0
Existing Manufacturers Marketing Product Outside the United States	6	0
New Applicants	0	1
Existing 510(k) Applicants	0	4
Total Number of 510(k) Submissions	8	5

2. Interactions Between FDA and Industry

i. Preparation Costs

PMA approvals are subject to pre-market and post-marketing requirements that are not required of 510(k) clearance, such as pre-market manufacturing site and clinical site inspections, annual report submission, stability studies, submission of institutional review board (IRB) approvals and informed consent forms, and notification of transfer of ownership. In addition, PMA supplements must be submitted for approval of changes to labeling, location and procedures related to a PMA. The proposed rule would require producers of devices for the detection of *M. tuberculosis* complex to obtain pre-market clearance (via 510(k) submission).

The estimated savings will be the difference between the cost of preparing and submitting a PMA and the cost of preparing and submitting a 510(k) application for new entrants, and the difference between the cost of a PMA supplement and the 510(k) for existing PMA holders. Blozan and Tucker (1986, Ref. 4.1) estimate the average cost of preparing a 510(k) at $500. Using Blozan and Tucker's sample, the average cost per page

is $21, or $36.63 after adjusting for inflation (Ref. 4.2). FDA records indicate that an original PMA and a PMA supplement would have approximately 8,000 pages and 850 pages, respectively. Moreover, based on similar medical device products, FDA estimates that new 510(k) submissions will consist of 3,000 pages. The estimated cost for the 510(k) would be $109,891 (=3,000*$36.63). FDA assumes the preparation cost of a PMA supplement is the same as FDA's review time ratio of a PMA supplement (180 days) and a 510(k) (90 days). This leads to an estimated preparation cost of $62,271 (=850*$36.63*2) for a PMA supplement. The best-supported prior FDA estimates on the cost of a PMA are approximately $1,000,000 (see 73 FR 7501), which adjusted for inflation is $1,018,781. Total preparation costs would be $5.36 million in the first year and $908,891 per year after year 1.

ii. Review-related Activities, Annual Reports and User Fees

There will also be savings in review costs. FDA estimates that the review time would decrease from a maximum of 180 days for a PMA supplement to a maximum of 90 days for a 510(k). It is estimated that review costs are $563,000 per PMA and $13,400 per 510(k) (Ref. 4.3). Updated to 2010 dollars, these costs are $643,805 per PMA and $15,323 per 510(k). Since the review time for a PMA supplement is twice that of a 510(k), we assume that the review cost for a PMA supplement is twice that of a 510(k), $30,646. The total savings in review time is approximately $3.80 million in year 1 and $628,482 per year after year 1.

Applicants of devices cleared under a 510(k) submission will not be subject to annual reporting requirements, which impose preparation costs on PMA holders and review costs on FDA. An average annual report includes 114 pages. Assuming that the preparation cost per page for an annual report is similar to a PMA supplement, the estimated cost savings per annual report equals $8,791 (=114*$73.26) in preparation costs and $30,646 in review-related costs. We estimate total savings in year 1 of $70,330 in preparation costs and $245,172 in review-related costs. After year 1, estimated total savings for preparation and review-related activities are $8,791 and $30,646,.

User fees are currently set at $220,050 for a premarket application, $4,049 for a 510(k) submission and $7,072 for annual report filings. We estimate total savings of $1.35 million in year 1 and $216,001 per year after year 1 in submission filing fees. Total savings related to annual report submission are estimated at $61,616 in year 1 and $7,702 per year after year 1.

iii. Inspection Costs

The average full cost of domestic device inspections are $30,900 for pre-market approval and $33,400 for post-market inspection. The total savings to FDA of inspecting sites would be $425,600 in year 1 and $64,300 per year after year 1.

ERG (2011, Ref. 4.4) estimates that the manufacturer hosting an inspection incurs a labor burden approximately twice that of the FDA investigator. Data indicate that on average it takes 89 hours for an FDA investigator to conduct an inspection. The Bureau

of Labor Statistics (May 2010, Ref. 4.5) reports that the mean wage for management occupations (occupational code 110000) in the "medical equipment and supplies manufacturing" industry (North American Industry Classification System, NAICS 339100) is $61.21. Accounting for benefits and overhead, this yields an average cost of hosting an inspection of $10,895 (= 89 * 2 * $61.21). The total savings in inspection-hosting cost is estimated at $152,535 in year 1 and $21,791 per year after year 1.

3. Unquantifiable Costs

FDA believes that the proposed special controls will prevent or mitigate an overall increase in the number of post-marketing events. The history of this product indicates that since the first PMA approval in 1995, there have been no recalls for this product code, and the only adverse event was reported in 1999. Inspections conducted in the last five years have led to two No Action Indicated (NAI) classifications, and two Official Action Indicated (OAI) classifications--one warning letter and one untitled letter. Since the 510(k) regulatory pathway does not require pre-market inspections, it is possible that such change could lead to an increase in adverse events, warning letters, untitled letters, or recalls. FDA does not have enough information to quantify costs arising from a potential increase in the risk associated with these events. Among other costs, an increase in adverse events could result in increased inspections to domestic and foreign sites, which would offset the estimated benefits.

With increased competition, the revenue of existing manufacturers might decrease. However, this loss in revenue will be offset by the gain in profits for new entrants who will share in the total market profits.

4. Summary and Discussion

Rule-induced savings associated with declassification appear in Table 2. Our estimates of the total savings in year 1 arising from interactions between FDA and industry are $11.49 million, while our annual estimates after year 1 are $1.89 million (see Table 2 below). Annualized over 20 years, the estimated savings is $9.4 million using a 3 percent discount rate, and $7.4 million using a 7 percent discount rate (see Table 3).

If there is an increase in the number of adverse events, recalls, untitled letters, and warning letters increases there could be costs that would reduce the estimated benefits. Future retrospective analysis would be needed to determine the magnitude of such impact.

Table 2. - Summary of Benefits

	Year 1	Annual, Post Year 1
Private Sector: Preparation Cost		
510(k) Submission	$5,358,105	$908,891
Annual Reports	$70,330	$8,791
Inspections (Hosting)	$152,535	$21,791
Subtotal	**$5,580,970**	**$939,473**
Private Sector: User Fees		
510(k) Submission	$1,353,924	$216,001
Annual Reports	$61,616	$7,702
Subtotal	**$1,415,540**	**$223,703**
Government (not funded by user fees)		
510(k) Submission	$3,801,537	$628,482
Annual Reports	$245,172	$30,646
Inspections	$452,600	$64,300
Subtotal	**$4,499,309**	**$723,428**
Total	**$11,495,820**	**$1,886,604**

Table 3. - Present Value and Annualized Value of Quantified Benefits

	Present Value ($ million)		Annualized Value ($ million)	
	3 percent	7 percent	3 percent	7 percent
Private Sector: Preparation Cost				
510(k) Submission	$17.8	$13.8	$1.2	$1.3
Annual Reports	$0.2	$0.2	$0.0	$0.0
Inspections (Hosting)	$0.2	$1.6	$2.3	$0.2
Subtotal	**$18.2**	**$15.6**	**$3.5**	**$1.5**
Private Sector: User Fees				
510(k) Submission	$20.1	$14.3	$1.4	$1.4
Annual Reports	$0.9	$0.7	$0.1	$0.1
Subtotal	**$21.1**	**$15.0**	**$1.4**	**$1.4**
Government				
510(k) Submission	$56.6	$40.3	$3.8	$3.8
Annual Reports	$3.6	$2.6	$0.2	$0.2
Inspections	$6.7	$4.8	$0.4	$0.5
Subtotal	**$66.9**	**$47.7**	**$4.5**	**$4.5**
Total	**$106.2**	**$78.2**	**$8.8**	**$7.4**

C. Regulatory Alternatives

1. No Regulation

The simplest alternative would be to leave the current regulations unchanged. Under this option, there would be no change in estimated benefits or potential costs. However, the increased cost to entry might deter potential improvements in market efficiency and new innovations.

2. Reclassification to Class I

An alternative to the proposed rule would be to reclassify devices for the detection of *M. tuberculosis* complex from class III to class I. While this alternative would further reduce the costs and hence the incentive for entry to the market, without special controls in place, it is uncertain that the product would be safe and effective. Specifically, this alternative could lead (i) to increased bio-safety risks to healthcare workers, (ii) to disease progression due to false negatives, and (iii) incorrect treatment due to false positives, which are mitigated by the special controls.

D. International Effects

Of the $626.0 million in sales from manufactures who currently hold a PMA, $82.4 million comes from manufacturers whose ultimate parent companies were not American. Fifty percent of the manufacturers who currently market a similar device outside the United States and who are likely to seek clearance is owned by a non-American company. Overall, FDA anticipates that one out of every four 510(k) submissions will come from a company whose ultimate parent company is not American. Foreign manufacturers would, if the proposed rule is finalized, benefit in a similar manner as domestic manufacturers. That is, there will be benefits associated with submitting a 510(k) rather than a PMA.

III. Regulatory Flexibility Analysis

The Regulatory Flexibility Act requires agencies to prepare a regulatory flexibility analysis if a proposed rule would have a significant effect on a substantial number of small businesses, non-profit organizations, local jurisdictions or other entities. Reclassification of this device from class III to class II will relieve manufacturers of the device of the cost of complying with the pre-market approval and post-marketing requirements, and may permit small potential competitors to enter the market by lowering their costs.

We estimate that the overall savings induced by the rule is $1.89 million per submission, of which $1.16 million will go to the firms. Under the Small Business Administration (SBA) definition firms in this industry would be considered small if they hire 500 employees or less. Using the SBA definition, at least 2 of the existing firms that market their product outside the United States would be considered small. For these firms, the potential savings would represent at least 4 percent of their total sales volume.

Moreover, small business entities whose sales are less than $100 million would qualify for FDA small business fees which could be up to 50 percent off the standard fees. Of the six manufacturers who currently market devices outside of the United States and who are likely to seek FDA clearance, three manufacturers would qualify for a small business fees, and will thereby further increase the estimated savings. Thus, FDA certifies that the final rule will not have a significant economic impact on a substantial number of small entities.

IV. References

4.1. Blozan, Carl F. and Steven A. Tucker. "Premarket Notifications: The First 24,000." *MD&DI* pp. 59-69. January 1986.

4.2. U. S. Department of Commerce, Bureau of Economic Analysis. National Income and Product Accounts Table 1.1.9 Implicit Price Deflators for Gross Domestic Product, http://www.bea.gov/national/nipaweb/SelectTable.asp, accessed March 25, 2011; National Income and Product Accounts Table 1.1.4. Price Indexes for Gross Domestic Product, http://www.bea.gov/national/nipaweb/SelectTable.asp, accessed February 23, 2012.

4.3. Geiger, Dale R. "FY 2003 and 2004 Unit Costs for the Process of Medical Device Review." September 2005. http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/Overview/MedicalDeviceUserFeeandModernizationActMDUFMA/ucm109216.pdf.

4.4. Eastern Research Group, Inc. "Profile of Baseline Materials Management Practices of Finished Drug Product Manufacturers: Draft Final Report." Contract No. 223-2008-10017I, Task Order 10. October 19, 2011.

4.5. U.S. Bureau of Labor Statistics, Occupational Employment Statistics. "May 2010 National Occupational Employment and Wage Estimates," http://www.bls.gov/oes/current/oes_nat.htm, accessed December 29, 2011; "May 2010 National Industry-Specific Occupational Employment and Wage Estimates," http://www.bls.gov/oes/current/naics4_334500.htm, accessed February 24, 2012.

4.6. U.S. Small Business Administration. "Table of Small Business Size Standards Matched to North American Industry Classification System Codes." November 5, 2010. http://www.sba.gov/sites/default/files/Size_Standards_Table.pdf, accessed February 24, 2011.