

FDA – Industry MDUFA IV Reauthorization Meeting
January 27, 2016; 9:40 am – 3:45 pm
FDA White Oak Building 66, Silver Spring, MD
Room 4404 and by WebEx*

Purpose

To discuss details of FDA’s integrated proposal package for MDUFA IV reauthorization.

Participants

FDA

Malcolm Bertoni	Office of the Commissioner (OC)
Marc Caden	Office of Chief Counsel (OCC)
Joni Foy	Center for Devices and Radiological Health (CDRH)
Sonja Fulmer	CDRH
Elizabeth Hillebrenner	CDRH
Louise Howe	OCC
Aaron Josephson	CDRH
Sheryl Kochman*	Center for Biologics Evaluation and Research (CBER)
Toby Lowe	CDRH
Thinh Nguyen	Office of Combination Products (OCP)
Brendan O’Leary	CDRH
Geeta Pamidimukkala	CDRH
Prakash Rath	Office of Legislation (OL)
Don St. Pierre	CDRH
Darian Tarver	OC
Peter Tobin	CDRH
Kim Worthington	CDRH
Jacqueline Yancy	CDRH
Barb Zimmerman	CDRH

Industry

Hans Beinke	Siemens (representing MITA)
Nathan Brown	Akin Gump (representing AdvaMed)
Phil Desjardins	Johnson & Johnson (representing AdvaMed)
Sergio Gadaleta	Becton Dickinson (representing AdvaMed)
Elisabeth George*	Philips (representing MITA)
Allison Giles*	Cook (representing MDMA)
Mark Gordon	Abbott (representing MDMA)
Megan Hayes	Medical Imaging Technology Alliance (MITA)
Donald Horton	Laboratory Corporation of America Holdings (representing ACLA)

Tamima Itani	Boston Scientific (representing MDMA)
Mark Leahey	Medical Device Manufacturers Association (MDMA)
John Manthei	Latham & Watkins (representing MDMA)
Michael Pflieger	Alcon (representing AdvaMed)
Jim Ruger	Quest Diagnostics (representing ACLA)
Paul Sheives*	American Clinical Laboratory Association (ACLA)
Patricia Shrader	Medtronic (representing AdvaMed)
Janet Trunzo	Advanced Medical Technology Association (AdvaMed)
Diane Wurzbarger	GE Healthcare (representing MITA)

Meeting Start Time: 9:40 am

Executive Summary

During the January 27, 2016, user fee negotiation meeting, FDA presented an integrated proposal combining elements of Industry's and FDA's proposals. FDA presented additional details on certain aspects of the proposal and emphasized each topic's importance to the Agency. Industry agreed to consider this discussion and integrated proposal, and to develop a counter proposal to present at the next meeting. Industry also reaffirmed its interest in quantifying efficiencies FDA would realize from some of the proposals and enhancements.

FDA's Integrated Proposal

FDA presented details and cost estimates for an integrated proposal that addresses issues important to Industry, FDA, and in some instances both. FDA reiterated the opportunities for MDUFA IV, including ensuring a consistent, predictable, and efficient review experience. FDA's proposal package bundled the proposals into several categories, including Infrastructure, Process Improvement, Innovation, and Performance.

FDA's Integrated Infrastructure Proposal

FDA's integrated infrastructure proposal included managerial retention and oversight, Quality Management, and IT modernization.

Managerial Retention and Oversight

To implement effective recruitment and hiring strategies, FDA proposed 6 FTE to further incorporate scientific and technical perspectives and best practices into recruitment activities throughout the hiring process.

To fully implement the Independent Assessment recommendations for review oversight and consistency, FDA believes additional managers are needed. FDA proposed 20 FTE to increase the capacity of Branch Chiefs to provide greater oversight of review procedures, to oversee

appropriateness and quality of deficiencies, and to allow Branch Chiefs the time for increased interactions with industry, such as through longer Pre-Submission meetings. FDA also proposed performance-based incentives to improve management retention.

Quality Management

FDA proposed 20 FTE to establish a Quality Management (QM) team composed of a director and two branches. One branch would be responsible for QM and Operational Excellence, including implementing a robust Corrective and Preventive Action (CAPA) system and development of knowledge management and document control procedures. The other branch would be responsible for measuring and monitoring quality through metrics development and analysis, program audits, and reporting. In response to questions from Industry, FDA indicated that they were proposing that the 20 FTE cover 16 for Office of Device Evaluation (ODE) and 4 for the Office of *In Vitro* Diagnostics and Radiological Health (OIR).

Industry asked clarifying questions about how QM is currently implemented within ODE. FDA explained that the proposal is to establish a new group that does not currently exist; currently, program operations and management conduct CAPA activities and audits. FDA explained that lack of dedicated staff to conduct QM activities causes stress to the review system because staff time and attention are diverted from other activities that support the review process. FDA also explained that the proposed structure is modeled after the quality management organization in the Patent and Trademark Office, which has a mature quality management system supporting a similar scientific and regulatory review program. FDA also explained, in response to a question from Industry, that QM staff would analyze and assess quality issue and coordinate reforms in response to those issues.

IT Modernization

FDA briefly discussed the IT Modernization proposal that was detailed during the meeting on December 15, 2015. This proposal encompasses the development of the myDevices Portal and eSubmitter within a cloud-based portal that would enable electronic submissions, structured data, and streamlined tracking. The proposed IT infrastructure includes the development of smart review templates and enhanced auditing capacity. FDA estimated \$2.5 million annually in special operating costs to develop the IT infrastructure, and noted an efficiency of up to \$2 million annually as the eSubmitter system is phased in. This cost estimate assumes the start-up costs for the IT improvements would be funded using \$6.5 million of user fees of the current MDUFA III carry-over balance.

FDA and Industry discussed the benefits of IT modernization, including consolidation of IT systems and creation of back-up processes and systems, improved daily processing, and cost savings from reduction in other contracts. Industry asked clarifying questions on the timing of eSubmitter implementation and noted the need to consider small business interests. Industry and FDA agreed to continue discussing the return on investment of this proposal.

The total cost of the Integrated Infrastructure proposal was estimated to be 46 FTE, including targeted recruitment specialists, managers to enhance review oversight and consistency, and the QM team. In addition, FDA estimated annual special operating costs of \$3.7 million, \$2.7 million, and then \$2.2 million each year for the final three years. These annual amounts include \$1.7 million per year in manager incentive pay, and a range of \$2 million down to \$0.5 million per year in IT costs, net of efficiencies that are fully realized in the third year of MDUFA IV.

Industry questioned what efficiencies might be gained through the establishment of the QM team and the increase in managerial oversight. FDA described the benefits of greater consistency in review decision making due to day-to-day managerial oversight and the capacity for system-level oversight by the QM team, allowing for a formal process to identify and address corrective actions as well as nonconformities. FDA and Industry discussed the importance of calculating or demonstrating a return on investment with respect to greater consistency, despite the challenges in developing appropriate and objective measures and data. FDA emphasized that a QM structure was identified as a key finding as part of the independent assessment conducted by Booz Allen Hamilton.

FDA's Integrated Process Improvements Proposal

FDA presented an integrated Process Improvements proposal, incorporating FDA's proposal for a more integrated review process model, Device Coordinators, Industry's proposals for sharing of Review Summaries, and other requested Process Improvements.

Integrated Review Process

FDA proposed shifting some compliance and surveillance activities into ODE to achieve a more integrated approach for the review of devices. FDA modeled this proposal after the approach that already exists in OIR. FDA suggested that the integrated review process could improve industry experience by streamlining the review of all aspects of a device's lifecycle within a single office. Furthermore, all issues for a submission would be reviewed by the same supervisory chain, and ODE could make process enhancements for PMA Approvable decisions, 513(g) submissions, post-approval studies, and other processes not currently within ODE. To fully implement an integrated review process model by the end of MDUFA IV, FDA estimated 8 FTE would be needed to establish appropriate management structure to oversee the newly integrated activities and 6 FTE for program operations staff to establish procedures and other resources and provide processes and tools to promote consistency. FDA further estimated \$0.15 million in the first year of MDUFA IV and \$0.05 million annually for the remaining years in special operating costs. Industry and FDA discussed why new managers would be needed for consolidating different functions within a single office.

FDA noted that the estimate for AdvaMed, MDMA and MITA's PMA proposal was 60 FTE. FDA described how the integrated review process proposal addresses the underlying issues from the PMA proposals with significantly less resources, although it does not establish the proposed

PMA quantitative performance goals. FDA noted that the scope of benefits includes a “no submission left behind” mechanism for post-Approvable letters and 513(g) submissions and the implementation of a performance target to issue the FDA decision within 60 days of a panel meeting. Industry asked clarifying questions about the proposal and the status of FDA’s ongoing program alignment efforts, and FDA explained how OIR adopted the integrated review process model.

Device Coordinators

FDA proposed to hire 43 FTE as Device Coordinators who would ensure consistency in process and feedback for each innovative device’s entire regulatory lifespan, from Pre-Submission through marketing authorization. Such additional coordination would be applied to all devices expected to be reviewed through the PMA or De Novo pathways. FDA explained that the Device Coordinators would be responsible for tracking the performance goals of the many review pathways, which have increased from fewer than 10 goals in MDUFA I to at least 33 goals in MDUFA III.

Industry questioned if there would be any efficiencies in reviewer workload through the establishment of Device Coordinators. FDA noted that although the Device Coordinators would be taking on some of the reviewer responsibilities, reviewers and managers currently have such a workload that the pressure to meet performance goals stresses the review system and adversely impacts FDA’s ability to provide a consistent review experience. The Device Coordinators would be serving as a relief valve for the reviewers and managers allowing for an improved review process.

Review Summaries Proposal

Based on Industry’s feedback from the meeting on January 20, 2016, FDA presented a revised proposal for review summaries based on the following assumptions: the review summary would be provided directly to the 510(k) sponsor within 21 days following the MDUFA decision; the content would be based on the lead reviewer’s memo, redacted by the lead reviewer for proprietary or confidential commercial information (CCI) and privileged deliberative information; the review summaries would be reviewed by disclosure staff prior to release; and, review summaries would be provided for all 510(k) submissions that receive a MDUFA decision. (FDA approximated the applicable submission volume at 3200 per year.) FDA estimated the cost of this proposal to be 15 FTE and \$1.5 million in Freedom of Information Act (FOIA) training costs.

FDA’s Integrated Performance Proposals

FDA presented proposals for the review of Q-Submissions, *de novo* Requests, and Third Party 510(k)s.

Q-Submissions

FDA proposed the following process for Pre-Submissions: Industry submits at least two proposed meeting dates in the Pre-Submission; within 15 days of receipt, FDA would accept one of the proposed meeting dates or provide two alternative meeting date options between day 30 and day 60; within 7 days of FDA's response, Industry would accept one of the proposed dates or request additional options; within 55 days or 5 days prior to the scheduled meeting (if the meeting occurs earlier than day 55), FDA would provide written feedback; within 14 days of the meeting, FDA would provide meeting minutes. Based on Industry's feedback, FDA modified their previous proposal to apply a "no submission left behind" mechanism if a meeting is not scheduled within 30 days, instead of applying the mechanism if a meeting is not held within 100 days. FDA estimated that 57 FTE would be needed to provide written feedback by day 55 (or 5 calendar days prior to the meeting). In response to FDA's proposal to take over responsibility for drafting meeting minutes, Industry noted that company performance in drafting minutes had improved significantly, and reiterated its preference to maintain that responsibility.

FDA also proposed that 13 additional FTE would support a performance goal for Submission Issue Meetings (SIMs) within 30 days.

To determine the costs for these proposals, FDA relied on the stated expectation of AdvaMed, MDMA and MITA that submission volumes in these areas would plateau at existing levels rather than continue to increase during MDUFA IV at or similar to the rate that submission volume increased during MDUFA III. FDA reiterated their concern that this workload may continue to increase. Therefore, FDA's proposal assumes that a workload uncertainty mechanism would be established to ensure that resources are sufficient to achieve the performance goals if workload assumptions used to determine the cost estimates do not hold. Additionally, these proposals would require \$0.6 million annually in IT costs.

De Novo

FDA provided a summary of the different *de novo* proposals during the negotiation meetings. FDA originally proposed that user fees be used to increase review capacity such that 70% of *de novos* would receive a decision within 120 days by the end of MDUFA IV. AdvaMed, MDMA, and MITA's original *de novo* proposal called for 90% of direct *de novos* to receive a decision in 120 days starting in the first year of MDUFA IV. At the January 20 negotiation meeting, FDA explained that achieving 90% performance in the first year of MDUFA IV is impractical (due to the time needed to hire and train staff, as well as the level of improvement that would be required over current performance levels) so FDA estimated costs for industry's proposal based on a modified target of 90% performance by the fourth year of MDUFA IV. FDA estimated this revised version of industry's proposal would cost 100 FTE and \$0.2 million annually in IT costs. During the January 27 meeting, FDA presented a second alternative proposal with steadily improving performance targets that would achieve a decision on 80% of *de novos* within 120

days by the final year of MDUFA IV. FDA estimated the cost of this proposal to be 61 FTE and \$0.2 million annually in IT costs.

Third Party 510(k) Review

FDA presented details on the proposal to strengthen the third party premarket review program. FDA suggested a primary solution of centrally tracking the scientific quality of the review memo through robust reviewer feedback tools, determining patterns in FDA deficiencies and letters with Additional Information requests and Not-Substantially Equivalent decisions, and developing audits for the application of cross-cutting and device-specific guidance documents. FDA proposed to use the results of this analysis to tailor training for FDA and third party reviewers. FDA further proposed to improve the third party review program by training third parties, providing redacted example reviews, auditing third parties, removing incompetent third parties, and tailoring the program to allow review of some submissions with clinical data while also providing mechanisms for FDA to limit third party review of some devices that are not well-suited to the program. Industry asked about the agency's current tools for addressing incompetent third parties, and FDA and Industry agreed further discussion would be needed on that issue. With dedicated resources to correct and maintain oversight of the program, FDA proposed steadily improving performance targets that would achieve decisions on 85% of Third Party 510(k)s within 30 days by the end of MDUFA IV. FDA described the benefits of an enhanced third party program in which the public and FDA have confidence, including transparency for manufacturers when selecting a third party and faster and more predictable time to market for devices. FDA estimated the cost of this proposal to be 17 FTE and a total of \$4.5 million in special operating costs over the course of MDUFA IV.

CLIA Waiver

FDA provided a cost estimate for meeting steadily increasing performance targets that would achieve the following goals on CLIA Waiver by Application submissions by the fourth year of MDUFA IV: 90% of Dual 510(k) and CLIA Waiver by Application submissions would receive a decision in 180 days, 90% of stand-alone CLIA Waiver by Application submissions without panel meetings would receive a decision in 120 days, and 90% of CLIA Waiver by Application submissions with panel meetings would receive a decision in 320 days. FDA provided a cost estimate for the proposal while noting that FDA's initial analysis indicates that there could be legal impediments to FDA using MDUFA funds to implement industry's CLIA proposal. FDA and Industry agreed that further analysis is needed before proceeding with this proposal.

FDA's Integrated Innovation Proposals

FDA presented proposals on Digital Health, Guidance Development, Leveraging Standards, Patient Input, and Real World Evidence.

Digital Health

FDA described a Digital Health proposal for consistent review of software and issues related to digital health. FDA proposed to streamline and align FDA processes with software lifecycles and to increase the number of experts available to support internal and external stakeholders. FDA noted that there have been inconsistencies in the identification of deficiencies in the review of software. FDA proposed a systematic, end-to-end evaluation and optimization of medical device software regulation. FDA further proposed to provide additional options for timely interactions with FDA earlier in the software development lifecycle to support software design and architecture decisions that can reduce regulatory burdens. The proposal includes efforts to better leverage data available to FDA to improve and streamline software testing and to enable more focused and tailored FDA premarket reviews. To implement this proposal, FDA estimated \$0.72 million annually and 13 FTE for process alignment, training, oversight, technical support, and international engagement with International Medical Device Regulators (IMDRF) efforts. In response to questions concerning recent hires for digital health and the role of these additional FTE, FDA indicated that these FTE would build up capabilities primarily within OIR.

Device-Specific Guidance

FDA noted that AdvaMed, MDMA, and MITA have expressed interest in a greater number of, and regular updates to, device-specific guidances. To address their request, FDA proposed to establish a new guidance model for streamlining device-specific guidance documents. FDA proposed to hire 12 FTE who would be primarily technical writers to produce high quality device-specific guidance documents more efficiently. FDA noted that implementing this model would leverage the time subject matter experts spend on device-specific guidance more effectively, and allow them more time to focus on premarket reviews, further supporting MDUFA goals and commitments. FDA explained the benefits of this proposal, including an increased number of device-specific guidance documents, finalization of draft device-specific guidances in a timelier manner, more relevant and up-to-date final guidance documents, and minimization of uncertainty related to data requests for devices that fall within the scope of the guidance.

ACLA noted that it had not expressed interest in an increased number of, or regular updates to, device-specific guidance documents.

Leveraging Standards

FDA presented a proposed accreditation scheme for conformity assessment of FDA-recognized consensus standards. FDA described the value to manufacturers in gaining greater certainty in the predictability of the review process through testing conducted via an accredited Certification Body (CB) program. FDA described the value to the Agency in having increased confidence in testing and conformity to consensus standards. FDA further described the value to the U.S. from a global harmonization perspective because the proposed accreditation CB program would

provide a national voice commensurate with other national and regional CB programs. FDA proposed to work directly with the testing labs and accreditation bodies to reduce premarket questions in areas where current conformity activities are met with inconsistent testing practices, conformance declarations, and regulatory review. The use of an FDA accredited CB program will also drive improvements in the development of and recognition of consensus standards and improve knowledge of postmarket evaluation of safety and performance due to a greater understanding of how the device was tested and evaluated. FDA provided an example of a Canadian conformity assessment framework and noted that other organizations, such as the Consumer Product Safety Commission (CPSC), currently have a conformity assessment framework.

FDA estimated the cost to implement this proposal to be 13 FTE and a total of \$4.7 million over MDUFA IV in special operating costs. FDA explained that this proposal would reduce regulatory burden, identify and fix non-conformity device issues earlier during development, and increase the predictability of premarket review. FDA further noted that this proposal would increase the consistency in data submitted in submissions, and that CDRH would save resources on the review of certain testing through increased confidence in standards. Industry questioned what the scope of this proposal would include. FDA discussed the intent to focus first on cross-cutting standards.

Real World Evidence

FDA provided additional rationale supporting the Real World Evidence (RWE) proposal intended to enable premarket reviewers to use RWE for premarket decision-making by building a system that links and improves the regulatory quality of RWE data sources, such as data from electronic health records, healthcare claims, and registries. FDA also described the long term goals of the RWE proposal, including greater use of the premarket-to-postmarket data shift and streamlined regulatory decisions. FDA noted that MDUFA is an appropriate mechanism for FDA and Industry to establish mutually beneficial goals and accountability for such goals. FDA reiterated the proposal is intended to create or improve upon existing “regulatory grade” registry modules that are linked to other data sources. For first-of-a-kind devices, FDA proposed to develop novel methodologies and apply existing methodologies for randomization within registries. FDA further proposed to establish and employ Objective Performance Criteria and Performance Goals for regulatory decision making for mature devices. FDA noted this proposal could generate efficiencies in Medical Device Reporting (MDR) requirements for PMA devices. FDA further noted that one intended outcome of the proposal is to minimize or obviate the need for traditional Post Approval Studies (PAS) as a condition of approval for many devices. FDA noted additional uses for many devices, including use of the data for labeling expansions, less time for completion of IDE studies, and the use of RWE as a comparator to data collected through traditional trials.

Industry raised concerns about the use of claims data because off-label use or use by clinical staff without appropriate training for the device could yield data that would be difficult to use for the proposed purpose. FDA noted that the proposal addresses that concern by evaluating the strengths, limitations, and the appropriate use of various RWE sources for informing regulatory actions. Industry also questioned the applicability of RWE to premarket uses; FDA reiterated the proposal's scope for the purpose of the user fee program is on premarket activities. FDA estimated the cost to implement this proposal to be 15 FTE and \$10 million annually.

Patient Input

FDA reiterated that information from patients can be useful during the benefit/risk evaluation of a device and provided details on potential commitments for the Patient Input proposal. FDA proposed to develop staff capacity to more efficiently and effectively review submissions that contain Patient Preference Information (PPI) and to support the development and review of Patient Reported Outcomes (PROs). FDA proposed for staff to work with public-private partnerships to develop patient preference studies in priority areas where decisions are preference-sensitive. FDA further proposed to train CDRH medical officers, scientific reviewers, and statisticians in PRO and patient preference study development and validation. FDA proposed to hold a public meeting to discuss how sponsors can incorporate PPI and PROs in their submissions. FDA also proposed that staff would be involved in writing guidance documents to clarify for industry how to use PPI and PROs in their submissions. FDA noted that these activities would allow for earlier detection and greater understanding of challenges that arise during review of PPI and PRO during device evaluation (as early as the Q-submission stage), quicker development of potential strategies to overcome these challenges, and greater consistency in FDA's approach to review, validation, and usage of PPI and PRO as part of the device evaluation process. FDA estimated the cost of this proposal to be 12 FTE and \$3.5 million over the five years of MDUFA IV.

Industry noted the need for FDA to make a distinction between PROs and PPI and noted that other organizations such as NIH are doing some overlapping work on PPI.

Discussion

FDA provided a summary of the cost estimate for FDA's integrated proposal. FDA estimated that the additional resources to implement such proposals over the five-year authorization period of MDUFA IV would total \$500 million, in addition to the base amount of user fees needed to maintain the level of staffing and other activities supported by MDUFA III user fees. FDA noted that these estimates do not contain inflationary adjustments.

FDA noted that the Integrated Process Improvements Proposal includes the previously presented proposal for the continuation of an Independent Assessment. FDA further noted that Industry's deficiency and modification proposals are included within the Management Oversight proposal.

Industry noted that the process enhancements and increased capacity reflected in the proposal package should result in additional efficiencies and presumably improvement in total time to decision, yet these did not appear to be reflected in FDA's presentation. Industry further noted that quality management and oversight could be applied to accountability regarding reviewer performance. Industry identified proposals that might result in efficiencies, such as the Device Coordinator and Management Retention and Oversight proposals that may reduce reviewer workload. FDA acknowledged these possibilities and reiterated the challenge in estimating efficiencies, as well as the need to reduce the current workload of overworked reviewers and managers.

Industry stated their intention to provide a counter proposal at the next negotiation meeting.

Next Meeting

The next meeting is scheduled for February 18, 2016.

Meeting End Time: 3:45 pm