**FDA – Industry MDUFA IV Reauthorization Meeting**
**December 15, 2015, 9:45 am – 4:00 pm**
**FDA White Oak Building 66, Silver Spring, MD**
**Room 4404**

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## Purpose

To discuss details of FDA's and Industry's proposal packages for MDUFA IV reauthorization.

## Participants

FDA

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| 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) |
| Prakash Rath | Office of Legislation (OL) |
| Don St. Pierre | CDRH |
| Darian Tarver | OC |
| Kim Worthington | CDRH |
| Jacquline Yancy | CDRH |
| Barb Zimmerman | CDRH |

FDA Subject Matter Experts (specialists participating on particular topics)

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| Nelson Anderson | CDRH |
| Patrick Axtell | CDRH |
| Kamal Elharam | CDRH |
| Paul Fisher | CDRH |
| Danica Marinac-Dabic | CDRH |
| Katie O'Callaghan | CDRH |
| Greg Pappas | CDRH |
| Annie Saha | CDRH |
| Peter Tobin | CDRH |

Industry

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| 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 Pfleger | Alcon (representing AdvaMed) |
| Paul Sheives | American Clinical Laboratories Association (ACLA) |
| Patricia Shrader | Medtronic (representing AdvaMed) |
| Janet Trunzo | Advanced Medical Technology Association (AdvaMed) |
| Diane Wurzburger | GE Healthcare (representing MITA) |

**Meeting Start Time:** 9:45 am

**Executive Summary**

During the December user fee negotiation meeting, FDA and Industry discussed the details of their respective proposal packages for MDUFA IV. FDA presented in-depth information for several proposals, including review process infrastructure, Q-submissions, *de novo*, CLIA waivers, patient-centered data, evidence from real world experience, and mechanisms for addressing workload uncertainty. FDA and Industry discussed questions and general observations about remaining proposals, but did not have a detailed discussion on these due to time constraints. FDA and Industry agreed to form working groups to further address some proposals that require focused work by subject matter experts.

**Industry Questions on FDA Proposals**

Prior to the December 15 meeting, AdvaMed, MDMA, and MITA provided questions to FDA on the proposals FDA presented in November. The first question focused on identifying resources that were saved as a result of MDUFA III programs that may offset future resource needs. FDA responded with two main points. First, on the general issue of efficiencies, FDA noted that this is a challenging area to analyze, and that the Agency had already identified some efficiencies in its MDUFA IV proposals by analyzing system-level synergies and economies of scale across proposals, as well as some reductions in level of effort that might accrue later in the MDUFA IV

period based on investments in process improvements early on. Moreover, FDA noted that additional efficiencies might be found, and expressed a desire to work through this analysis jointly with Industry as the structure of the MDUFA IV package takes shape. The second main point FDA made in response to the first question was to note that FDA agreed to the MDUFA III package based on specific identified efficiencies that were already built into the program design. FDA believes that any additional efficiencies that have been realized in MDUFA III, including those identified through the Independent Assessment, have allowed FDA to provide high performance across many program areas, from which Industry is already benefitting. FDA addressed the additional questions posed by AdvaMed, MDMA, and MITA through discussion of the proposal details.

**Review Process Infrastructure**

FDA presented details of its proposal to improve review process infrastructure, including proposals on personnel recruiting, management oversight and retention, quality management, and electronic submissions. FDA views these proposals as the foundation that is necessary to ensure a more consistent and predictable review experience. FDA proposed to hire recruiting specialists who would have more scientific and technical expertise than existing process-oriented human resources staff. The recruiting specialists would build relationships with external sources of talent to improve the talent pipeline and to support the review of job applications and resumes to identify the most technically qualified candidates. FDA also proposed that user fees fund retention incentives for supervisors. FDA further proposed reducing the reviewer to manager ratio from 11:1 to 8:1, a ratio FDA believes is necessary to recruit and retain supervisors and to improve oversight and consistency of review activities.

Industry questioned whether FDA has conducted sufficient benchmarking against other organizations to better understand recruitment strategies; FDA responded that they have done benchmarking and would be pleased to continue to work with Industry to identify a greater range of best practices for recruiting. Industry also expressed concern that the recruiting specialists would not resolve issues that job candidates have navigating the application process through the Office of Personnel Management (OPM). Industry and FDA discussed establishing a working group to further explore the issues identified in this proposal.

FDA also proposed to establish a dedicated Quality Management (QM) team, whose responsibilities would include implementing a robust Corrective and Preventive Action (CAPA) system and conducting systematic audits to minimize submission review variation among reviewers and branches. FDA noted that this proposal aligns with AdvaMed, MDMA, and MITA's proposal for analysis of reasons for withdrawals and analysis of conversions of Special 510(k)s to Traditional 510(k)s. FDA further proposed that the QM team would work with management on process improvements to enhance supervisory oversight of the premarket review process, including areas identified by AdvaMed, MDMA, and MITA, such as new premarket review data requests, communications impacting the review clock, withdrawals, and conversions

of Special 510(k)s to Traditional 510(k)s. FDA noted that additional discussion is needed to address AdvaMed, MDMA, and MITA's proposals on deficiencies traced to references and sponsor access to review summaries. FDA's proposal for the QM team responsibilities also included the establishment of a management system for controlled premarket process documents, such as SOPs, work instructions, and templates.

Industry asked clarifying questions on the purpose of the managerial oversight proposal and its relation to the Independent Assessment. FDA explained that the proposal to establish a QM team goes beyond the recommendations from the Independent Assessment, which was to identify and monitor critical control points in the review process. FDA noted that the QM team proposal is intended to establish additional Standard Operating Procedures (SOPs) and a feedback mechanism, in order to identify non-conformities.

FDA presented details on the eSubmission/myDevices proposal. FDA described the proposal to develop myDevices and eSubmitter within a cloud-based portal that would enable submission tracking. The proposed system would further allow the development of eReviewer, which would populate the reviewer's template and provide a streamlined mechanism to support a more consistent and efficient review process. FDA noted that the system would increase the quantity, quality, and timeliness of auditable data sets; facilitate reporting on submissions, including differentiation between Special and Traditional 510(k), Laboratory Developed Tests (LDTs), and CLIA reporting. FDA noted that this also addresses ACLA's proposal to enable separate reporting for LDTs. FDA further noted that the system would allow linking between pre-submissions and subsequent submissions, which in addition to the other reporting functions, addresses the proposal from AdvaMed, MDMA, and MITA. FDA subject matter experts presented a demonstration of myDevices, during which Industry asked several clarifying questions. FDA explained that the myDevices portal would support many different technologies and submission types. FDA noted this proposal would reduce Industry submission costs and would generate efficiency by reducing the FDA Document Control Center contract as the system is phased in.

FDA noted that per the proposal from AdvaMed, MDMA, and MITA, an independent assessment may be continued to determine the progress towards consistency in decision-making and further implementation of a quality management system. FDA noted the need to clarify the scope of any proposed new independent assessment.

**Q-Submissions**

FDA presented details on the Q-Submission proposal, including specific components addressing Pre-Submissions, Submission Issue Meetings (SIMs), and complex submissions. FDA noted the general sense of the value of Pre-Submissions, the steady increase in volume, and that they are the subject of proposals by FDA and AdvaMed, MDMA, and MITA. FDA presented a revised Q-Submission proposal to address issues raised by both proposals. FDA proposed the following

process improvements for Pre-Submissions: Industry submits two proposed meeting dates with the Pre-Submission; within 15 days of receipt, FDA would conduct a Refuse to Accept (RTA) review of the Pre-Submission and either reject the submission, 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 RTA 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 sooner, FDA would provide written feedback; within 14 days of the meeting, FDA would provide meeting minutes; and by 100 days, FDA would apply a "no submission left behind" mechanism to all open submissions.

FDA identified additional opportunities to enhance the consistency, predictability, and timeliness of SIMs. FDA noted the value of the SIM program, for which submission volume is growing, as an opportunity for timely, in-depth dialogue to resolve deficiencies related to submissions that are not on FDA's review clock, such as when the submission is on hold. FDA noted that the SIM program facilitates timely, positive decisions in fewer review cycles, which would not be possible without discussion. FDA proposed a working group to discuss details of the SIM program, including defining SIM, in order to continue the timely feedback provided through SIMs, increase the predictability in the process with performance goals for meetings within 30 days, and enhance auditing capabilities for additional insight into the program.

FDA also discussed AdvaMed, MDMA, and MITA's proposal on Pre-Submissions to allow for longer than one hour meetings for complex submissions based on transparent and consistent standards. Industry pointed out that in some cases it may be more efficient to have one longer meeting rather than multiple, staggered meetings. FDA noted that complex submissions may benefit from additional dialogue. FDA and Industry agreed to establish a working group.

FDA proposed a revised goal structure for Q-Submissions, incorporating the proposal of AdvaMed, MDMA and MITA and feedback on FDA's original proposal. FDA proposed that user fees be provided to increase review capacity such that written pre-meeting feedback be sent to the Sponsor 5 calendar days prior to the meeting for 90% of meetings by the end of MDUFA IV. FDA also proposed that user fees be provided to increase review capacity such that 95% of SIMs can be completed within 30 days by the end of MDUFA IV. FDA noted that the proposed goal structure ensures timely feedback and predictability in process while providing flexibility in scheduling. FDA further noted that the proposed performance ramp up is logistically necessary and reduces the total FTE cost over the 5 year program as compared to the proposal of AdvaMed, MDMA and MITA. In addition to the proposed performance goals for Q-Submissions, FDA further proposed to update IT systems used for workload management and quarterly reporting, in order to account for the additional performance goals and Q-Submission processes.

FDA noted that myDevices would provide key enhancements for these submissions, by the creation of a platform to facilitate meeting scheduling and enhanced auditing abilities, allowing

linkage to future submissions. FDA further described the anticipated value of Q-Submissions and related Review Process Infrastructure enhancements, noting that a structured process will increase predictability and consistency; enhanced review capacity will enable FDA to meet performance goals that ensure timeliness; supervisory oversight will enhance consistency in substance of feedback; additional tracking capabilities will enable audits; and longer meetings for complex submissions may provide efficiencies to Industry sponsors.

Industry asked clarifying questions on the Pre-Submission proposal and provided suggestions for the number of days for the various targets. FDA and Industry agreed to establish a working group to address technical issues regarding the Pre-Submission and SIM proposals.

**De Novo**

At the November meeting, FDA and AdvaMed, MDMA, and MITA presented proposals for the review of *de novo* requests. During the December meeting, FDA described the need to shorten review times for *de novo* requests, noting that currently available resources are insufficient for CDRH to consistently fulfill the statutory deadline of 120 day review for all *de novos*. FDA noted that the program has reached a tipping point based on the volume of submissions and insufficient targeted resources. FDA presented a revised proposal for the review of *de novo* requests. FDA's previous proposal considered Substantive Interaction (SI) and Missed MDUFA Decision (MMD) to ensure success, using a very similar structure to the 510(k) program established in MDUFA III. FDA's proposed performance ramp up is logistically necessary and reduces total FTE cost over the 5 year program as compared to the proposal of AdvaMed, MDMA and MITA. FDA proposed that user fees be provided to increase review capacity such that 85% of *de novo* requests receive SI within 75 days, and 70% of *de novos* can be completed within 120 days, by the end of MDUFA IV. Although the proposal presented by AdvaMed, MDMA, and MITA included a separate performance goal for post-not-substantially-equivalent (post-NSE) decision *de novos*, FDA noted that this is not a priority for the Agency due to the low (and decreasing) number of post-NSE decision *de novo* requests.

FDA compared this proposal to that of AdvaMed, MDMA, and MITA, who proposed that 90% of direct *de novos* receive a decision in 120 days. Although the latter proposal called for the performance goals to take effect in the first year of MDUFA IV, in order to estimate the resources needed for this proposal, FDA assumed that this performance is reached by the end of MDUFA IV, with an incremental increase of 10% in performance each year. FDA estimated that, given this assumption, the *de novo* proposal by AdvaMed, MDMA, and MITA would require more effort and resources than FDA's approach. FDA did not provide an estimate of resources for improving performance of post-NSE decision *de novos*, noting that the additional IT cost to track this performance goal would not be cost-effective.

FDA noted that benefits to Industry from FDA's *de novo* proposal include enhanced predictability, timeliness, decrease in total review time, establishment of a framework for future

product development for many small business *de novo* requestors, and additional tracking capabilities to enable audits. Industry asked clarifying questions on the *de novo* review process and the assumptions that FDA made to estimate the costs of the proposals. FDA and Industry agreed to discuss the proposals for the review of *de novo* requests in more detail during working group discussions.

**CLIA Waiver**

FDA presented a counter proposal to AdvaMed, MDMA, and MITA's November 18 proposal on the review of Clinical Laboratory Improvement Amendments (CLIA) waivers. FDA noted that with additional resources, it would be possible to reduce the timeframes for the review of CLIA waivers, although uncertainty exists as to the volume of submissions FDA will receive. FDA estimated the cost of both proposals based on AdvaMed, MDMA and MITA's projection for CLIA waiver workload. AdvaMed, MDMA, and MITA's proposed goals include a 95% goal to receive a decision in 90 days on CLIA waiver single submissions without a panel meeting, a 95% goal to receive a decision in 120 days on CLIA waiver dual submissions without a panel meeting, and a 95% goal to receive a decision in 320 days on CLIA waiver submissions with a panel meeting. FDA's counter-proposal includes review time goals to reach a MDUFA decision in 120 days on CLIA waiver single submissions without a panel meeting, 180 days on CLIA waiver dual submissions without a panel meeting, and 320 days on CLIA waiver submissions with a panel meeting. FDA proposed a ramp-up from 70% to 90% performance over MDUFA IV for these review time goals.

FDA estimated that AdvaMed, MDMA, and MITA's proposal would require a greater level of effort than FDA's counter proposal.

FDA's proposal incorporated AdvaMed, MDMA, and MITA's proposed process improvements, including release of guidance on CLIA waiver dual submissions, increased reporting and implementation of MMD, and also proposed implementation of RTA. FDA indicated that IT improvements would be needed under both proposals to support Dual reviews (which are manually tracked now), to implement RTA and MMD, and to allow for better tracking of CLIA related files, including Pre-Submissions. Improved IT would provide for enhanced oversight of feedback provided on CLIA waiver studies in Pre-Submissions. FDA and Industry agreed to form a working group to further discuss the details of the proposals for the review of CLIA waivers.

**Patient-Centered Data**

FDA presented a detailed proposal on improved predictability, consistency, and a "quality journey" for submissions with patient-centered data. FDA described how patient perspectives can inform various stages in medical device Total Product Life Cycle (TPLC), with a particular focus on (1) including patient reported outcomes (PROs) during clinical studies and (2) including patient preferences to inform FDA's benefit-risk assessment during the regulatory review phase.

FDA noted that industry submissions are seeking to use PROs to inform benefit-risk assessments for devices through pre-specified primary, secondary, or exploratory endpoints in premarket studies, or through postmarket evaluation. For patient preference information (PPI), FDA described how these data can be used in several major ways during benefit-risk assessments: (1) to identify the most important benefits and risks from a patient perspective, which can inform selection of primary and secondary endpoints, particularly in new technology areas; (2) to clarify how patients think about tradeoffs between benefits and risks, which can inform minimum acceptable benefit or effect size, which can impact study size; (3) to understand how patient preferences may vary across a population, which can inform patient subgroup considerations for benefit-risk assessments.

FDA noted that there has been an increase of more than 300% in premarket submissions containing PROs. More than 130 unique companies (small, mid-size, and large public companies) across product areas in all review divisions have submitted PROs in Investigational Device Exemption (IDE) applications and CDRH currently has no dedicated expertise, training, or programmatic support related to PROs or PPI. FDA proposed to improve the consistency, predictability, and efficiency of PRO-related review by hiring staff dedicated to PRO review, PRO training, and development of a policy for including PROs in device labeling. FDA further proposed to improve the "quality of the journey" for submissions involving PROs by using the dedicated expertise to identify and troubleshoot common challenges related to PRO review, and by the agency developing a PRO validation approach with a flexible framework for PROs used for different purposes, such as primary vs. secondary vs. exploratory endpoints. FDA also proposed to advance the state of the science of PROs and PPI by developing an efficient model for using "bridging studies" to more efficiently validate existing PROs for use in additional and/or broader populations, and by supporting development of PROs and PPI studies in critical areas.

Industry noted that PROs are a complex issue that may not be relevant to a broad cross-section of the industry, and expressed concern over the time required to validate a PRO and cost-benefit profile. FDA noted that PROs are a cross-cutting scientific area which has been observed across every premarket division, and the number of studies with PROs have been increasing substantially over the past 5+ years. PROs are also increasingly of interest in international markets and to hospital and health system administrators. FDA believes a targeted investment can improve the issues identified by industry. FDA noted that by making a modest investment into a program, FDA and industry could significantly improve efficiency and predictability for review of high impact submissions containing PROs and PPI. Such improvements could be directed through a MDUFA commitment which specifies a programmatic focus on troubleshooting common issues, and by FDA developing approaches to improve predictability, specifically for including PROs in labeling, and outlining a flexible framework for determining that PROs are sufficiently validated for a given use. FDA believes a modest targeted investment in such a program would result in a more predictable and efficient review process for high

impact submissions containing PROs and PPI. Additionally, FDA believes targeted investments will lead to reduced time and cost when development and validation of new PROs or use of PROs in expanded populations is needed.

**Evidence from Real World Experience**

FDA provided details on its proposal to leverage real world evidence (RWE) for device evaluation. FDA identified opportunities to have streamlined and less expensive regulatory decision-making based on the best available data from clinical settings, to make data from the entire product lifecycle available for premarket review, to improve the quality of data to "regulatory grade" for use in the premarket context, and for targeted investments to improve patient access through greater use of premarket to postmarket data shifts while maintaining standards of safety and effectiveness. FDA noted that MDUFA investments could be used to develop methodologies and infrastructure that would enable the use of national registries, as well as data from electronic health records and health care claims that could lead to faster and less expensive medical device development and marketing submission review. FDA noted that many manufacturers are already supporting the registry network approach, including leveraging national registries for post-approval studies, a continued access study, a labeling expansion study, and postmarket surveillance studies.

FDA stated that the benefits of a system to improve use of RWE include fewer standalone studies, more efficient patient enrollment, less costly patient follow-up, harmonization with other national and international data, and greater use of premarket/postmarket data shifts. FDA proposed an investment in more efficient and better quality registries to build the robust regulatory apparatus that is needed to utilize RWE to streamline device evaluation and support innovation, which could bring devices to market faster.

Industry acknowledged that RWE has merit in advancing public health and raised questions on how broadly applicable the system would be to device manufacturers.

**Workload Uncertainty**

FDA briefly explained the Agency's proposed approach to develop a mechanism to address workload uncertainty. FDA discussed how the current MDUFA structure carries substantial performance risk because fees are set to support performance commitments based on assumed future workload levels, yet if future submissions are significantly higher than projections, the workload will outpace capacity, and performance will drop. FDA noted that potential workload increases could be driven by policy changes in areas such as LDTs and combination products. FDA noted that the current "fee offset" provision does not take into account increases in workload, hence increases in fee-based marketing submissions could drive fee over-collections while simultaneously increasing workload, yet FDA would have to give back the over-collections in the final year of the reauthorization period, making those resources unavailable to increase review capacity. FDA proposed to establish a mechanism for addressing this potential

problem by developing a model that signals significant departures in actual versus projected workload levels. FDA proposed to establish transparent workload projections associated with the negotiated MDUFA IV agreement. FDA further proposed to modify the statutory language to reduce the amount of "fee offset" when triggering conditions are met, and if necessary, increase fees to ensure resources are available and allocated in a targeted way to maintain performance. FDA proposed to engage a small working group of FDA and Industry participants to focus on model development to determine which workload categories should be included in the model, to establish baseline assumptions for projected workload and model weights, and to test the model using different workload and financial impact scenarios. In addition, FDA proposed to establish objectives for independent assessment of the mechanism for MDUFA IV.

Industry raised questions on how the proposed workload adjuster would function if the workload decreased and agreed to discuss this proposal further in a working group.

**Discussion**

Due to time constraints, FDA and Industry did not discuss several remaining proposal topics, including 510(k) total time to decision reduction, Third Party 510(k) review, Digital Health, leveraging standards, device-specific guidance, PMA process enhancements and total product life cycle, access to review summaries, and deficiencies traced to references. FDA noted that they had provided some requested data on 513(g) submissions prior to the meeting, and acknowledged that AdvaMed, MDMA, and MITA may present a 513(g) proposal at the next negotiation meeting.

FDA and Industry discussed establishing working groups to address technical details regarding personnel recruitment, IT (myDevices/eSubmitter), complex topics for Pre-Submissions, Pre-Submissions/SIMs, *de novo*, CLIA waivers, mechanisms for addressing workload uncertainty, and the PMA proposals. FDA and Industry agreed to work out the working group logistics over the next couple weeks, with the goal of holding technical working group discussions in early January and reporting out the key discussion points at the next negotiation meeting.

**Next Meeting**

The next meeting is scheduled on January 20, 2016.

**Meeting End Time:** 4:00 pm