United States Government Accountability Office

Report to Congressional Requestors

December 2017

FDA MEDICAL DEVICE REVIEWS

Evaluation is Needed to Assure Requests for Additional Information Follow a Least Burdensome Approach

Accessible Version

GAO-18-140

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GAO Highlights

Highlights of GAO-18-140, a report to congressional requestors

Why GAO Did This Study

Determining that a new medical device is safe and effective is a substantial investment of time and resources for the sponsor and FDA, the agency that regulates medical devices. FDA relies on the device sponsor to provide supporting data at the time of its original submission, and the agency can request additional information during the review. The Federal Food, Drug, and Cosmetic Act, as amended, requires that when FDA requests additional information from sponsors, the agency consider the least burdensome means of evaluating a medical device.

GAO was asked to provide information on FDA's implementation of the least burdensome requirements in its medical device review process. This report (1) describes FDA's requests for additional information and sponsor disagreements, (2) describes its least burdensome training efforts, and (3) describes FDA actions to improve its requests for additional information and examines the extent to which it has evaluated its implementation of the least burdensome requirements. GAO reviewed FDA documents and guidance and interviewed agency officials. GAO also interviewed officials from four relevant medical device manufacturing associations.

What GAO Recommends

GAO is making one recommendation that FDA develop and use performance metrics to evaluate the implementation of the least burdensome requirements. The Department of Health and Human Services agreed with GAO's recommendation.

View GAO-18-140. For more information, contact Marcia Crosse at (202) 512-7114 or crossem@gao.gov.

What GAO Found

Since 1997, the Food and Drug Administration (FDA) has been required to consider the least burdensome means of evaluating certain types of medical devices for marketing, including when requesting that sponsors—generally manufacturers—seeking to market their medical devices provide information in addition to what was provided in their submissions. GAO found that, from 2001 through 2016, FDA issued letters asking sponsors to provide such information for a majority of the more than 62,000 medical device submissions that it reviewed. Sponsors may formally disagree with the request on the grounds that it is not the least burdensome method needed for FDA to review the submission. For example, sponsors appealed FDA decisions internally to agency management 63 times from 2013 through 2016, and of these, FDA identified 33 such appeals in which the sponsor raised an issue related to least burdensome requirements. FDA agreed or partially agreed with the sponsors in 11 of these appeals. Medical device industry representatives noted that these appeals may not fully represent the number of such disagreements, because applicants are generally concerned that an appeal would damage their relationship with FDA and potentially negatively affect future device applications.

FDA provided staff training that was specifically dedicated to addressing the least burdensome requirements from 1997 through 1999. Since 1999, FDA has not offered a course dedicated to the least burdensome requirements, but has incorporated related concepts into other training programs, such as in a training mandatory for most new reviewers. In response to the 21st Century Cures Act, enacted in 2016, FDA is providing new least burdensome training to all relevant employees, and said that 80 percent had received the training as of October 2, 2017. Although FDA did not specifically evaluate the effectiveness of past training on least burdensome requirements, it is implementing an evaluation of all device-related training, including the new least burdensome training. It also plans to complete a required audit of training on least burdensome requirements by June 2018.

FDA has not specifically evaluated implementation of the least burdensome requirements. However, in response to broader evaluations, such as an independent assessment of its medical device review process, the agency is in the early stages of developing processes that may improve its requests for additional information. For example, FDA plans to conduct an audit of letters requesting additional information. FDA is developing the audit's methodology and expects it will assess whether the agency's process was followed. However, due to their early stage, the extent to which these efforts will allow FDA to assess implementation of the least burdensome requirements is unclear. In 2002, FDA stated that it planned to periodically assess the implementation of the least burdensome principles, and federal internal control standards identify the importance of performance metrics for such assessments. However, the agency has yet to develop performance metrics to do so. Until such measures are developed and used, FDA will not be able to evaluate whether it effectively and consistently applies a least burdensome approach in its medical device reviews.

Contents

Abbreviations

AI	additional information
CDRH	Center for Devices and Radiological Health
FDA	Food and Drug Administration
FDAMA	Food and Drug Administration Modernization Act of 1997
HHS	Department of Health and Human Services
MDUFA III	Medical Device User Fee Amendments of 2012
MDUFA IV	Medical Device User Fee Amendments of 2017
PMA	premarket approval

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December 15, 2017

The Honorable Lamar Alexander
Chairman
Committee on Health, Education, Labor, and Pensions
United States Senate

The Honorable Richard Burr
United States Senate

The Food and Drug Administration (FDA), within the Department of Health and Human Services (HHS), is responsible for ensuring that medical devices sold in the United States provide reasonable assurance of safety and effectiveness and do not pose a threat to public health.[1] Making this determination represents a substantial investment of time and resources for both FDA and the device sponsor, generally the manufacturer. For example, in 2014, FDA reviewed about 4,100 submissions from sponsors seeking to market their medical devices, and each review ranged from an average of 125 days for lower-risk devices to an average of 330 days for higher-risk devices.[2] In making its assessment, FDA relies on the sponsor to provide supporting data at the time of its initial premarket submission and may thereafter request additional data in the course of the review to obtain sufficient evidence supporting the safety and effectiveness of the medical device. However, any request for additional information has the potential to impose undue burden on the sponsor and delay the review of the device, and sponsors may opt to formally disagree with the necessity of the requested information.

Given the resource investment involved in getting a medical device to market, as well as the public health need, efforts have been made to streamline the decision-making process without compromising scientific integrity or FDA's ability to protect the public health. For example,

[1]Medical devices range from simple tools, such as bandages and surgical clamps to complicated devices, such as pacemakers. Generally, medical devices include items used for the diagnosis, cure, mitigation, treatment, or prevention of a disease. See 21 U.S.C. § 321(h). Throughout this report, the term device refers to a medical device that is not being regulated as a drug or a biological product.

[2]Review times are for fiscal year 2014, the most recent data available. FDA, *FY 2016 Performance Report to Congress for the Medical Device User Fee Amendments* (Silver Spring, Md.: September 2016).

Congress has already taken several steps to reduce unnecessary burdens associated with the medical device review process. For certain types of premarket submissions, federal law requires FDA to utilize the "least burdensome" means possible in certain elements of the review processes of medical devices.[3] FDA has laid out broad principles in guidance interpreting how those statutory provisions apply throughout its reviews.[4] In 2016, Congress required FDA to provide training for appropriate staff on the meaning and implementation of the statutory least burdensome requirements and conduct periodic assessments of implementation to ensure that the least burdensome requirements are fully and consistently applied.[5]

You asked us to provide information on FDA's implementation of the least burdensome requirements, as well as any training FDA has done to ensure staff are aware of the statutory requirements. This report

1. describes FDA requests for additional information to support medical device reviews and how least burdensome requirements were related to sponsor disagreements about these requests,
2. describes FDA efforts to ensure that its employees are trained on the least burdensome requirements, and
3. describes the steps FDA has taken to improve its requests for additional information and examines the extent to which it has evaluated its implementation of the least burdensome requirements.

To describe FDA requests for additional information to support medical device reviews and how least burdensome requirements were related to sponsor disagreements about these requests, we analyzed agency documents, such as FDA's guidance for industry and staff on the least burdensome provisions and FDA's annual performance reports. For fiscal year 2001 through fiscal year 2016, the years for which FDA had reliable data, we analyzed counts of medical device submissions received and reviewed by FDA, as well as FDA's requests for additional information from medical device sponsors. We also reviewed internal appeals and

[3]See 21 U.S.C. §§ 360c(a)(3)(D)(ii), 360c(i)(1)(D)(i)), 360e(c)(5).

[4]See Food and Drug Administration, *The Least Burdensome Provisions of the FDA Modernization Act of 1997: Concept and Principles; Final Guidance for FDA and Industry* (Rockville, Md.: Oct. 4, 2002).

[5]See 21st Century Cures Act, Pub. L. No. 114-255, § 3058(a), 130 Stat. 1033, 1128 (2016) (codified at 21 U.S.C. § 360c(j)).

disputes of FDA decisions submitted by sponsors that FDA identified as being related to the least burdensome requirements. Information on internal appeals was limited to the period from May 2013 through fiscal year 2016.[6] To assess the reliability of data FDA provided, we interviewed knowledgeable agency officials, conducted quality checks to identify any obvious errors, and compared the detailed data FDA provided to us with summary data that FDA had publicly reported on its website. We determined these data were sufficiently reliable for the purposes of our reporting objective. We also reviewed a non-generalizable sample of requests for additional information FDA issued to sponsors during the medical device review process.[7] We interviewed FDA officials from the Center for Devices and Radiological Health (CDRH) responsible for reviewing medical devices. We also interviewed representatives of the medical device industry to obtain the industry's perspectives on how the least burdensome provisions have been involved in FDA's requests for additional information.[8]

To describe FDA efforts to ensure that its employees are trained on the least burdensome requirements, we asked FDA to identify any training activities for medical device review staff that related to the least burdensome requirements since they were first established with the enactment of the Food and Drug Administration Modernization Act of 1997 (FDAMA).[9] For certain of those activities, we examined the specific

[6]FDA officials told us that, prior to May 2013, the agency did not have a formal mechanism to track internal appeals of significant decisions and, accordingly, did not have a comprehensive list of such appeals.

[7]We reviewed a sample of 73 requests—known as deficiency letters or additional information (AI) letters—that FDA issued from 1997 through 2016. To obtain examples across years and FDA review types, we asked FDA to provide at least 2 letters from each year 1997 through 2016, with at least 1 related to a premarket approval (PMA) and 1 related to a premarket notification, known as a 510(k), from each year. Medical devices are generally subject to one of two types of FDA premarket review processes. The PMA process, the most stringent type of premarket review, requires the sponsor to submit evidence providing reasonable assurance that the new device is safe and effective. The 510(k) process requires the sponsor to demonstrate to FDA that the new device is substantially equivalent to a device already legally on the market, and therefore, does not require a PMA.

[8]We interviewed representatives from four organizations that represented the medical device industry during its discussions with FDA: The Advanced Medical Technology Association, the Medical Device Manufacturers Association, the American Clinical Laboratory Association, and the Medical Imaging and Technology Alliance.

[9]Pub. L. No. 105-115, 111 Stat. 2296 (1997) (codified as amended at 21 U.S.C. §§ 301 et seq.).

course materials so we could further illustrate how these materials referred to the least burdensome requirements. We also reviewed documentation describing FDA evaluations of this training, as well as planned evaluations. We interviewed FDA officials about how training on the least burdensome requirements had changed and about the planned changes to least burdensome training and training evaluations.

To describe the steps FDA has taken to improve its requests for additional information and examine the extent to which it has evaluated its implementation of the least burdensome requirements, we reviewed relevant statutes and guidance that set out relevant requirements for both reviewers and sponsors outlining FDA's implementation of the least burdensome requirements and its plans for evaluation of that implementation. We also reviewed documentation describing, and spoke with relevant FDA officials about, performance metrics that the agency uses to monitor its implementation of the least burdensome requirements and evaluations the agency had conducted or planned to conduct. We compared the extent to which FDA has evaluated its implementation of the least burdensome requirements with federal standards for internal control.[10]

We conducted this performance audit from November 2016 to December 2017 in accordance with generally accepted government auditing standards. Those standards require that we plan and perform the audit to obtain sufficient, appropriate evidence to provide a reasonable basis for our findings and conclusions based on our audit objectives. We believe that the evidence obtained provides a reasonable basis for our findings and conclusions based on our audit objectives.

[10]GAO, *Standards for Internal Control in the Federal Government* (GAO-14-704G). Internal control is a process effected by an entity's oversight body, management, and other personnel that provides reasonable assurance that the objectives of an entity will be achieved.

Background

FDA Medical Device Review Process

FDA classifies each medical device type intended for human use into one of three classes based on the level of risk it poses to the patient or the user and the controls necessary to reasonably ensure its safety and effectiveness.[11] Examples of types of devices in each class include the following:

- Class I: tongue depressors, elastic bandages, reading glasses, and forceps;
- Class II: electrocardiographs, powered bone drills, and mercury thermometers; and
- Class III: pacemakers and replacement heart valves.

Before medical devices may be legally marketed in the United States, they are generally subject to one of two types of FDA premarket review processes.[12]

- Premarket approval (PMA) process: Class III device types are typically required to obtain FDA approval through the PMA process.[13] Under this process, the medical device sponsor must submit an

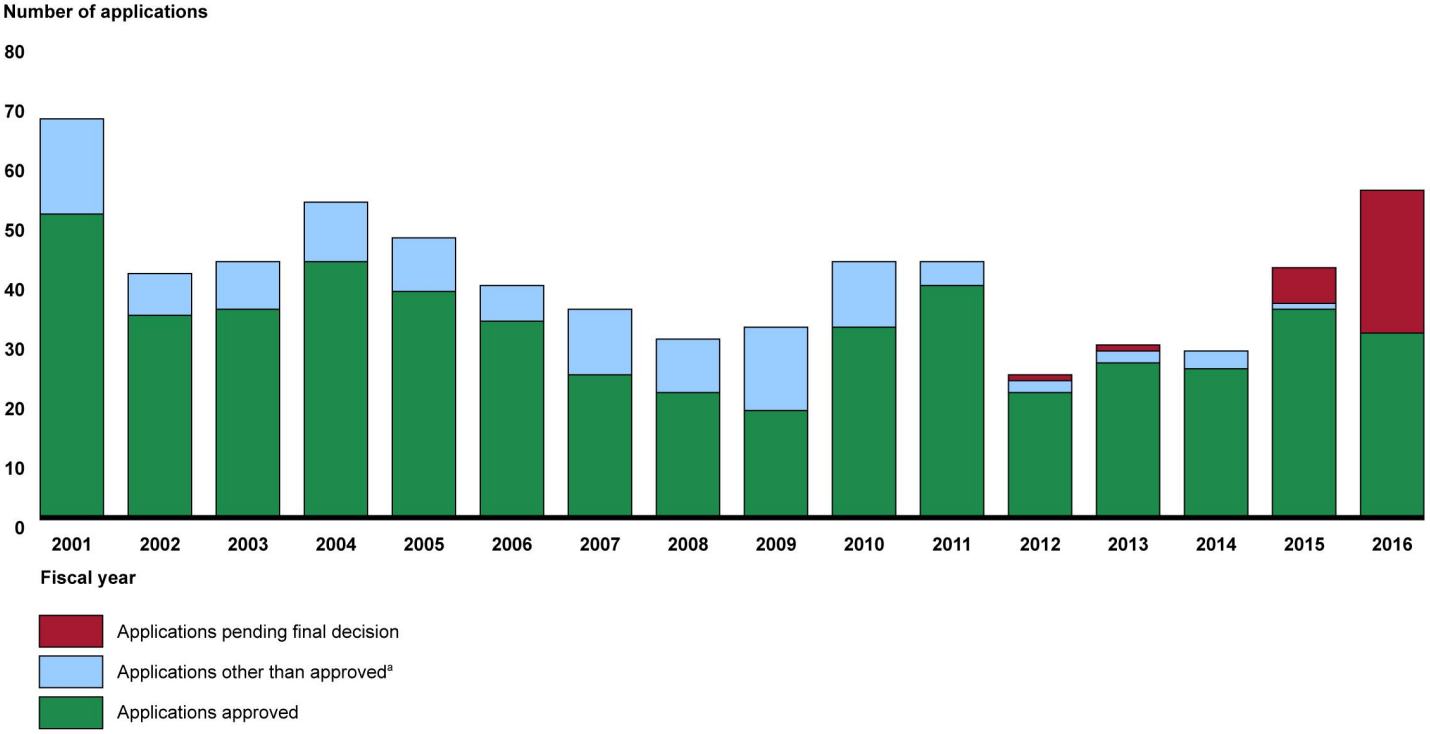
[11]Class I devices are those for which compliance with general controls, such as good manufacturing practices specified in FDA's quality system regulation, are sufficient to provide reasonable assurance of their safety and effectiveness. Class II devices are subject to general and special controls, such as postmarket surveillance. Class III devices are those (1) for which insufficient information exists to determine whether general and special controls are sufficient to provide reasonable assurance of the safety and effectiveness of the device and (2) that support or sustain human life or are of substantial importance in preventing impairment of human health, or that present a potential unreasonable risk of illness or injury. See 21 U.S.C. § 360c(a)(1) and 21 C.F.R. § 860.3(c) (2017).

[12]A small percentage of devices enter the market by other means, such as through the humanitarian device exemption process, which allows market entry, without adherence to certain requirements, for devices benefiting patients with rare diseases or conditions. See 21 U.S.C. § 360j(m) and 21 C.F.R. pt. 814, subpt H (2017).

[13]The requirements and procedures for submitting an application for premarket approval can be found at section 360e of title 21 of the U.S. Code. Premarket approval is not required for class I or class II devices or certain exempted devices such as those intended for investigational use that meet applicable requirements in 21 C.F.R. pt. 812. See 21 U.S.C. § 360e(a).

application that includes—among other things—full reports of investigations, typically including clinical data, providing reasonable assurance that the new device is safe and effective. The PMA process is the most stringent type of premarket review. A successful application results in FDA's approval to market the device. From 2001 through 2016, medical device sponsors submitted 651 PMA applications, and FDA approved for marketing 506 of those submissions. (See fig. 1.)

Figure 1: Original Medical Device Premarket Applications Approved by FDA, 2001 to 2016



Source: GAO analysis of Food and Drug Administration (FDA) data. | GAO-18-140

Note: Applications were counted according to the fiscal year in which the application was received by FDA, even if an approval or another decision occurred in a subsequent fiscal year.

[a]Applications with a decision other than approved may include applications that reached a "not approvable" decision or were otherwise withdrawn.

- Premarket notification, or 510(k), process: Most medical devices requiring premarket review are subject to FDA's premarket notification or 510(k) process.[14] This includes class I and II device types that are

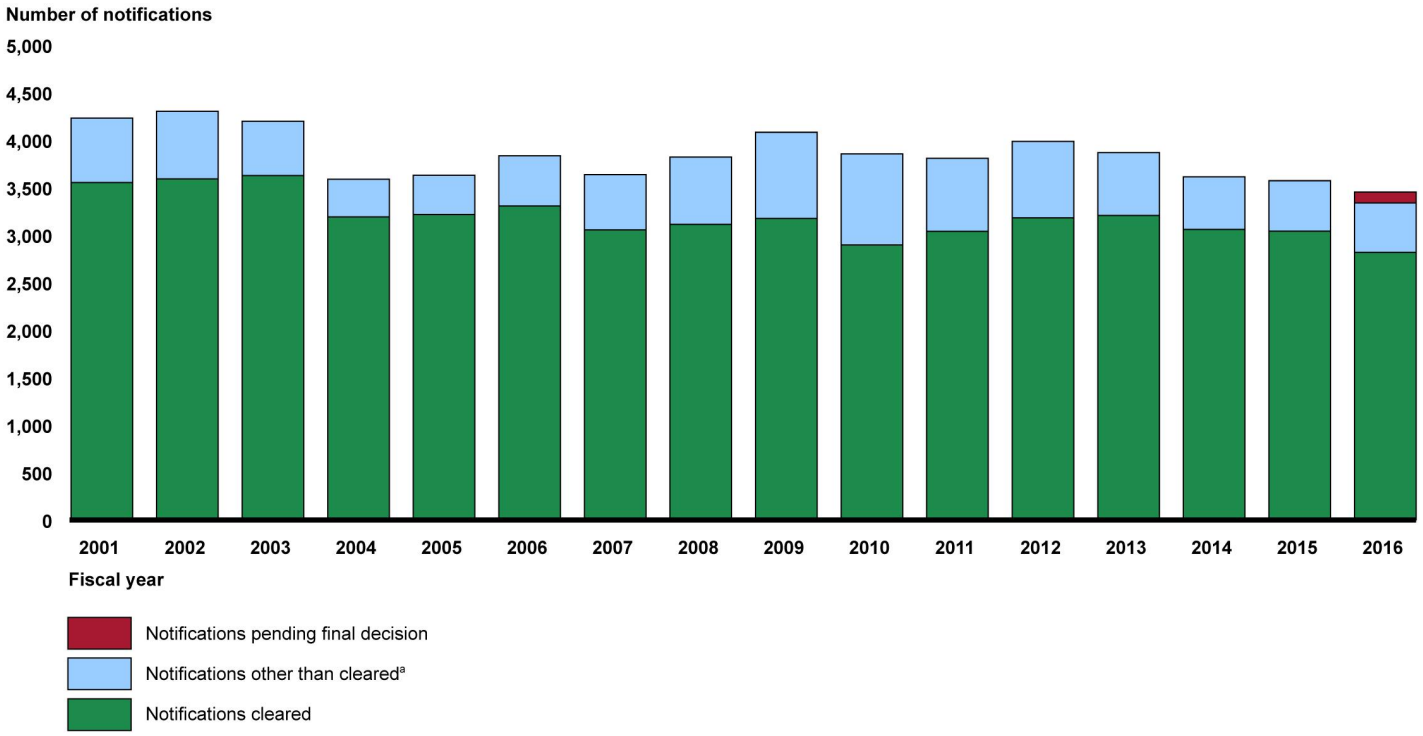
[14]See 21 U.S.C. § 360(k).

not specifically exempted from the 510(k) notification requirement.[15] Under this process, the medical device sponsor must notify FDA at least 90 days before it intends to market a new device and demonstrate to FDA that the new device is substantially equivalent to a predicate device, and therefore does not require a PMA.[16] For most 510(k) notifications, clinical data are not required and substantial equivalence will normally be determined based on comparative descriptions of intended device uses and technological characteristics, and may include performance data. A successful 510(k) submission results in FDA's clearance to market the device. From 2001 through 2016, medical device sponsors submitted 61,439 premarket notifications and FDA cleared 51,028 devices for market. (See fig. 2.)

[15]See 21 U.S.C. §§ 360(l), (m). See also section .9 of 21 C.F.R. pts. 862 to 892, e.g., 21 C.F.R. §§ 862.9, 864.9 (2017) (defining the limitations of the exemptions).

[16]Under federal regulations, a predicate device can be a device that (1) was legally marketed prior to May 28, 1976; or (2) was marketed on or after May 28, 1976, and was found to be substantially equivalent to a legally marketed device through the 510(k) premarket notification process; or (3) was reclassified by FDA from class III to class II or I. 21 C.F.R. § 807.92(a)(3) (2017). *Substantial equivalence* or *substantially equivalent* means that the proposed device has the same intended use as the predicate device and the same technological characteristics as the predicate device or has different technological characteristics and information submitted to FDA demonstrates that the proposed device is as safe and effective as the predicate device and does not raise different questions of safety or effectiveness. 21 U.S.C. § 360c(i)(1)(A).

Figure 2: 510(k) Medical Device Notifications Cleared by FDA, 2001 to 2016



Source: GAO analysis of Food and Drug Administration (FDA) data. | GAO-18-140

Note: Notifications were counted according to the fiscal year in which the notification was received by FDA, even if a clearance or other decision occurred in a subsequent fiscal year.

[a]Notifications categorized as other than cleared were determined not substantially equivalent or were withdrawn, deleted, or not cleared due to another reason.

During premarket review under both the PMA and 510(k) processes, FDA and the medical device sponsor may engage in an interactive process. To start, there may be a pre-submission meeting between FDA and the sponsor, during which the parties discuss the upcoming review and try to resolve potential obstacles for approval or clearance. Then, FDA receives the premarket submission, makes a determination to accept or not accept the submission, and assigns a reviewer. In making its assessment whether to approve, or clear, a submission, FDA relies on the sponsor to provide supporting data as part of the submission. However, the agency can request additional information in the course of the review in order to make a determination of reasonable assurance of safety and effectiveness, or of substantial equivalence. This additional information can be obtained through informal interactions, such as a phone call or email. Alternatively, for more significant issues, FDA may make a more formal request for additional information, known as a deficiency letter in

the case of a PMA application and additional information (AI) letter for a 510(k) notification. FDA will issue such requests if the submission lacks significant information necessary for FDA to complete its review, and the agency will request the sponsor amend the submission to provide the necessary information regarding the device.

If a sponsor disagrees with an FDA regulatory decision concerning a medical device submission, including a CDRH employee's decision to request additional information or a significant decision regarding approval or clearance of a medical device, it can take multiple actions.[17] Specifically, a sponsor can, among other things, (1) contact the CDRH Ombudsman for assistance, (2) file an internal appeal of an FDA decision, or (3) request that the disagreement be resolved through CDRH's Medical Device Dispute Resolution Panel, as described below.[18]

- Ombudsman: According to FDA's guidance, prior to the agency reaching a regulatory decision, the most effective means of resolving a dispute between CDRH and an external stakeholder is through discussion and agreement. The CDRH Ombudsman is available to assist in clarifying issues, mediate meetings and teleconferences, and conduct discussions with the parties in an effort to resolve disagreements short of a formal review or internal appeal.
- Internal Appeal: Once FDA makes a regulatory decision, a sponsor can request a supervisory review of that decision, which we refer to as an internal appeal.[19] For this process, the supervisor of an FDA employee will, at the request of a medical device sponsor, review a decision or action of the employee and issue a decision. The decision rendered by the supervisor, acting as the review authority, customarily

[17]CDRH has defined the term "significant decision" to include decisions about premarket approval and substantial equivalence at the final stage of review (e.g., a not substantially equivalent or substantially equivalent in the case of a 510(k) submission, or an approval, not approvable, or denial in the case of a PMA submission). See FDA, *Center for Devices and Radiological Health Appeals Processes: Questions and Answers About 517A - Guidance for Industry and Food and Drug Administration Staff* (Rockville, Md.: Sept. 29, 2017).

[18]FDA offers several processes for medical device sponsors and other individuals outside of the agency to have decisions or actions taken by CDRH to be reviewed or reconsidered, including internal appeals, the Medical Devices Dispute Resolution Panel, petitions, and hearings. See generally, FDA, *Center for Devices and Radiological Health Appeals Processes - Guidance for Industry and Food and Drug Administration Staff* (Rockville, Md.: May 17, 2013).

[19]This internal appeals process is outlined in 21 C.F.R. § 10.75 (2016).

takes one of the following forms: overturning the decision of the employee; upholding the employee decision; or, in some circumstances, referring the matter back to the employee for reconsideration under defined conditions.

- Medical Device Dispute Resolution Panel: If the dispute remains unresolved, the sponsor may request that FDA convene the Medical Device Dispute Resolution Panel. The panel is intended to provide a means for independent review of a scientific controversy or dispute between a sponsor and FDA, and make a recommendation to the Center director. According to FDA's guidance, the panel is primarily intended to address scientific controversies rather than other issues such as regulatory, legal, or statutory authority disputes.

As part of its commitments associated with the Medical Device User Fee Amendments of 2012 (MDUFA III), FDA agreed to participate in an independent, comprehensive assessment of the medical device submission review process.[20] Acting on recommendations from the contractor that conducted the assessment, FDA established working groups for each submission type, including PMAs and 510(k)s, which studied existing review processes and made recommendations.[21] In August 2017, the Medical Device User Fee Amendments of 2017 (MDUFA IV) reauthorized FDA's medical device user fee program, and FDA committed to another independent assessment.[22] FDA has

[20]See Pub. L. No. 112-144, tit. II, 126 Stat. 993, 1002 (2012). See also FDA, *MDUFA III Commitment Letter*, 12. A significant portion of FDA's annual appropriation for premarket medical device review and other activities consists of amounts derived from user fees paid by device manufactures. FDA was first authorized to collect medical device user fees in 2002 under the Medical Device User Fee and Modernization Act (P.L. 107-250) and Congress has reauthorized the user fee program every 5 years to provide additional resources for certain FDA oversight activities. These fees are collected and available for obligation only to the extent and in the amount provided in advance in appropriations acts. In association with each user fee authorization, FDA has committed to performance goals—specific time frames within which FDA is to take action on submissions—and other actions related to the review of medical device submissions. These commitments are negotiated between FDA and industry stakeholders and submitted to congressional committees prior to each reauthorization.

[21]Booz Allen Hamilton, *Independent Assessment of FDA Device Review Process Management: Deliverable 6: Final Implementation Evaluation Report for the Food and Drug Administration,* a report prepared at the request of the Food and Drug Administration, February 1, 2016.

[22]FDA Reauthorization Act of 2017, Pub. L. No. 115-52, tit. II (Aug. 18, 2017). See also FDA, *MDUFA Performance Goals and Procedures, Fiscal Years 2018 Through 2022*, 21.

committed to hiring a contractor to conduct this assessment by the end of December 2017 with a second phase to begin in 2020.

FDA Least Burdensome Requirements

In 1997, FDAMA added a requirement that the agency use the least burdensome approach during certain parts of PMA and 510(k) reviews.[23] These requirements were intended to reduce unnecessary burdens associated with the premarket approval and clearance processes; however, they did not lower the statutory criteria for demonstrating a reasonable assurance of safety and effectiveness or substantial equivalence. While the language in FDAMA differs slightly for the PMA and 510(k) processes, in both instances FDA was directed to consider the "least burdensome" means of requesting information needed for its review. Specifically, FDAMA requires that when the agency specifies data that must be submitted as part of a PMA application, the agency must consider the least burdensome appropriate means of evaluating device effectiveness that would have a reasonable likelihood of resulting in approval.[24] The agency must similarly consider the least burdensome appropriate means of demonstrating substantial equivalence when requesting information under the 510(k) notification process.[25] In both cases, FDA is statutorily required to request only information that is necessary to support the determination that there is reasonable assurance of effectiveness or substantial equivalence, respectively.[26]

[23]See Pub. L. No. 105-115, §§ 205(a)-(b), 111 Stat. 2296, 2336-7 (1997) (codified as amended at 21 U.S.C. §§ 360c(a)(3)(D)(ii), 360c(i)(1)(D)(i)).

[24]21 U.S.C. § 360c(a)(3)(D)(ii) ("Any clinical data, including one or more well-controlled investigations, specified in writing by the Secretary for demonstrating a reasonable assurance of device effectiveness shall be specified as result of a determination by the Secretary that such data are necessary to establish device effectiveness. The Secretary shall consider, in consultation with the applicant, the least burdensome appropriate means of evaluating device effectiveness that would have a reasonable likelihood of resulting in approval.").

[25]21 U.S.C. § 360c(i)(1)(D)(i) ("Whenever the Secretary requests information to demonstrate that devices with differing technological characteristics are substantially equivalent, the Secretary shall only request information that is necessary to making substantial equivalence determinations. In making such request, the Secretary shall consider the least burdensome means of demonstrating substantial equivalence and request information accordingly.").

[26]21 U.S.C. §§ 360c(a)(3)(D)(iii), 360c(i)(1)(D)(ii).

Subsequent laws have clarified the least burdensome requirements. In 2012, the Food and Drug Administration Safety and Innovation Act clarified that the term "necessary" means the minimum required information that would support either a determination that a PMA application provides reasonable assurance of the effectiveness of the device or a determination, for a 510(k) notification, of substantial equivalence between a new device and a predicate device.[27] In 2016, the 21st Century Cures Act added a provision applying the least burdensome concept to FDA's requests for additional information in the PMA process.[28] The law also applied the least burdensome concept to significant decisions, such as denials of PMA applications, requiring such decisions to include a brief statement regarding how least burdensome requirements were considered and applied.[29] Additionally, the law mandated each FDA employee involved in premarket submission reviews, including supervisors, to receive training on the least burdensome provisions, and required the agency to conduct an audit of the training, among other things, no later than June 2018.[30]

Although FDA officials have noted that the least burdensome principles are broad and could apply to all activities within the PMA and 510(k) premarket review process, they noted that the requests for additional information represent a key juncture for the application of least burdensome requirements. According to agency officials and industry representatives, the requests for additional information—deficiency letters in the case of PMAs and AI letters for its 510(k) reviews—are when FDA and the sponsor could disagree on whether the requested information is necessary for the agency to reach a final decision on the medical device under review.

[27]See Pub. L. No. 112-144, § 602, 126 Stat. 993, 1051 (2012) (codified as amended at 21 U.S.C. §§ 360c(a)(3)(D)(iii), 360c(i)(1)(D)(ii)).

[28]See Pub. L. No. 114-255, § 3058(b), 130 Stat. 1033, 1129 (2016) (codified at 21 U.S.C. § 360e(c)(5)).

[29]See Pub. L. No. 114-255, § 3058(c), 130 Stat. 1033, 1129 (2016) (codified at 21 U.S.C. § 360g-1(a)(3)).

[30]See Pub. L. No. 114-255, § 3058(a), 130 Stat. 1033, 1128-9 (2016) (codified at 21 U.S.C. § 360c(j)).

FDA Implementation of the Least Burdensome Requirements

Following the enactment of FDAMA in 1997, FDA went through a process in collaboration with the medical device industry to define the least burdensome concept and develop an approach to implement the provisions. Based on this, FDA released multiple guidance documents related to least burdensome requirements from 2000 through 2002.

- In November 2000 guidance, FDA outlined a four-part approach—referred to as "four-part-harmony" by FDA staff—for communicating deficiencies to medical device sponsors in accordance with the least burdensome requirements.[31] The guidance helps reviewers describe deficiencies identified in submissions in ways that are direct, concise, and complete, thus ensuring a more effective use of reviewers' and sponsors' time, effort, and resources. It also provides a suggested format for sponsors to respond to FDA. FDA updated this guidance in September 2017.[32]
- In 2002 guidance, FDA described its principles for implementing the least burdensome requirements and its activities to assess implementation.[33] The guidance outlines FDA's interpretation of the least burdensome concept as described in FDAMA, and explains its application to activities associated with PMA and 510(k) reviews. The guidance also states that FDA was in the process of developing tools to be used by both agency staff and its stakeholders to periodically assess the implementation of the least burdensome principles. It noted some measurement tools had already been developed and that

[31]FDA, *Guidance for Industry and FDA Staff: Suggested Format for Developing and Responding to Deficiencies in Accordance with the Least Burdensome Provisions of FDAMA* (Rockville, Md.: Nov. 2, 2000). The guidance recommends communicating deficiencies in four parts: (1) Clearly identify the specific issue or question; (2) Acknowledge the information submitted and explain why the information provided did not adequately address the issue; (3) Establish the relevance of the request to the PMA determination of "reasonable assurance of safety and effectiveness" or a 510(k) determination of "substantial equivalence;" (4) Request the necessary additional information needed to adequately address the issue and, when possible, suggest alternate ways of satisfying the issue.

[32]FDA, *Developing and Responding to Deficiencies in Accordance with the Least Burdensome Provisions Guidance for Industry and Food and Drug Administration Staff* (Rockville, Md.: Sept. 29, 2017).

[33]FDA, *Least Burdensome Provisions: Concept and Principles*, 2002.

additional tools were also needed to assess the impact of the least burdensome approach on expediting the development of new medical technologies.

In addition, FDA has included language about those requirements in other guidance documents. For example, in 2014, FDA issued guidance on the 510(k) program that describes how the least burdensome principles may affect the type of information necessary to demonstrate substantial equivalence at different decision points in the review of a 510(k).[34]

FDA Frequently Requested Additional Information to Support Medical Device Reviews, and Sponsor Disagreements Often Related to Least Burdensome Requirements

FDA Issued Deficiency and Additional Information Letters for a Significant Proportion of PMAs and 510(k)s

FDA requested sponsors provide additional information for a majority of the PMAs and 510(k)s it reviewed. For the period 2001 through 2016, FDA issued a large number of deficiency and AI letters relative to the number of submissions, although there was variation annually.[35] For PMAs, the number of deficiency letters as a percentage of new PMA applications submitted ranged from about 54 percent to 113 percent annually, or 82 percent on average, from 2001 through 2016. For the years 2006 through 2010, this percentage, as well as the total number of letters was higher, and FDA issued more deficiency letters than there were PMA applications submitted. Similarly, AI letters as a percentage of total 510(k) notifications received ranged from about 58 percent to more

[34]FDA, *The 510(k) Program: Evaluating Substantial Equivalence in Premarket Notifications: Guidance for Industry and Food and Drug Administration Staff* (Rockville, Md.: July 28, 2014).

[35]FDA deficiency and AI letters often identified more than one deficiency in each letter and the information FDA requested varied. For example, in one letter to a PMA sponsor, FDA expressed concern with the safety and effectiveness data, and requested that a study include a larger sample size with a longer window for following up with participants after the study. In a letter to a 510(k) sponsor, FDA requested additional drawings of the device, as the drawings provided with the initial submission did not illustrate all device components.

than 174 percent annually, or about 106 percent on average, from 2001 through 2016. While the number of 510(k) notifications remained similar across the time period we examined, from 2009 through 2012, the number of AI letters issued each year was, on average, nearly double the number in other years. During this period, FDA issued more AI letters than there were 510(k) notifications submitted. Since 2014, these percentages have been lower for both PMAs and 510(k)s.

FDA officials acknowledged the historical increase in the number of deficiency and AI letters and noted the more recent decrease. The officials attributed this decrease to a number of changes the agency agreed to in MDUFA III. For example, FDA implemented a policy to review submissions for administrative completeness prior to accepting the submission. They said this allowed the agency to limit deficiency and AI letters to issues related to the quality of the data provided and the studies conducted in support of the submission rather than to administrative issues. Also as a result of MDUFA III, the agency implemented an interactive review process to increase informal interaction between FDA and applicants and to minimize the number of review questions communicated through deficiency and AI letters. (See table 1.)

Table 1: Medical Device Submissions Received and FDA Requests for Additional Information, 2001 through 2016

Fiscal year	Original premarket applications (PMA)			510(k) notifications		
	Applications received	FDA information requests (deficiency letters)	FDA information requests as a percentage of applications	Notifications received	FDA information requests (additional information letters)[a]	FDA information requests as a percentage of notifications
2001	67	36	54	4,229	2,599	61
2002	41	29	71	4,301	2,477	58
2003	43	29	67	4,195	2,859	68
2004	53	46	87	3,585	2,647	74
2005	47	32	68	3,627	3,128	86
2006	39	43	110	3,832	3,891	102
2007	35	37	106	3,634	4,354	120
2008	30	34	113	3,819	5,164	135
2009	32	34	106	4,080	6,257	153
2010	43	45	105	3,852	6,692	174
2011	43	41	95	3,805	6,300	166
2012	24	21	88	3,983	6,193	155
2013	29	25	86	3,866	3,411	88
2014	28	17	61	3,610	2,962	82
2015	42	29	69	3,570	2,996	84
2016	55	37	67	3,389	2,993	88
Total	**651**	**535**	**82**	**61,377**	**64,922**	**106**

Source: GAO analysis of Food and Drug Administration (FDA) data. | GAO-18-140

Note: In this table, requests for additional information are included in the fiscal year that the related applications or notifications were received, even if the requests were issued in a subsequent fiscal year. Data for fiscal years 2009, 2012, 2013, 2015 and 2016 include some submissions that are still under review and therefore FDA had not issued final deficiency or additional information letters for each submission.

[a]FDA did not have counts of additional information letters readily available. Therefore, for each year, it provided the percentage of 510(k) notifications that are known to have received one, two, three, or four additional information letters. We used the percentages to calculate an estimated number of additional information letters.

We identified changes in how the deficiency letters and AI letters referenced the least burdensome requirements. Based on our sample of 73 letters from 1997 through 2016, FDA included an explicit acknowledgment of the least burdensome requirements in the letters issued from 2001 through 2009. However, based on our review, this practice ended in 2010, and later letters did not include this standard

language.[36] Representatives from the medical device industry told us that including the least burdensome language in the deficiency letters was a good practice because it raised awareness of the least burdensome principles. In September 2017, FDA released updated deficiencies guidance that, according to FDA officials, instructs staff how to better articulate the reason that the information is needed in accordance with the least burdensome requirements.[37] This guidance does not set forth boilerplate language regarding the least burdensome requirements for use in deficiency letters, but does include examples of well-constructed deficiencies, definitions for major and minor deficiencies, and a statement that FDA will attempt to resolve minor deficiencies interactively.

Though Data are Limited, Least Burdensome Requirements were a Significant Contributing Factor in Disagreements Raised by Medical Device Sponsors

The least burdensome requirements were often a significant contributing factor in disagreements raised by medical device sponsors, according to FDA officials and available FDA data. According to FDA, the most effective means of resolving disagreements is through discussion and mediation, and to that end, the Ombudsman's office is routinely involved in discussions between firms and medical device reviewers during the review process. For example, in 2016, the CDRH Ombudsman was involved with PMA and 510(k) medical device reviews 360 times out of 3,444 submissions. Although the agency was unable to identify which of these interactions were related to least burdensome requirements, agency officials told us that a substantial number likely resulted from a difference of opinion between the applicant and FDA on the appropriate level of scientific evidence, a portion of which likely have a least burdensome component.

[36]FDA also stopped including boilerplate language on the least burdensome requirements in its guidance documents in November 2009. According to agency officials, the language had been included inconsistently in past guidance documents, and officials concluded it was more important to articulate least burdensome principles than to merely include stock language about the least burdensome requirements.

[37]FDA, *Developing and Responding to Deficiencies in Accordance with the Least Burdensome Provisions Guidance for Industry and Food and Drug Administration Staff*, Sept. 29, 2017.

The least burdensome provisions were also frequently related to issues that applicants raised during internal agency appeals of FDA decisions of PMA and 510(k) reviews. Although FDA did not have readily available data on appeals that occurred prior to 2013, the agency was able to provide information about the 63 appeals of significant decisions that occurred from 2013 through 2016.[38] Of these 63 appeals, FDA identified 33 appeals—2 related to PMAs and 31 related to 510(k)s—in which the issue identified by the sponsor was related to least burdensome principles. According to medical device industry representatives, sponsors may not always pursue an appeal, so the number of official appeals may not represent the extent of least burdensome-related issues that sponsors experience. They said the sponsor may determine it is best to avoid conflict that could complicate future device submissions and comply with the request for additional information, even if it disagrees.

Of these 33 appeals, FDA agreed, or partially agreed with the sponsor for 11 appeals, which resulted in FDA overturning the decision or reopening the file and continuing the review. For the remaining 22 appeals, the agency upheld the initial reviewer decision. The following presents examples of appeals where the issue identified by the sponsor was related to the least burdensome requirements.

- In one appeal related to a 510(k) review, the sponsor objected to the reviewer's finding that the device was not substantially equivalent to a device already on the market. The sponsor stated that it had provided sufficient data for a substantial equivalence determination, and the FDA reviewer's request for additional risk mitigation measures and supplemental testing was unwarranted and inappropriate. The review authority determined that, while the information provided in the 510(k) premarket submission was not sufficient to establish substantial equivalence, some of FDA's requests were unwarranted. As a result of the appeal, FDA reopened the file and provided the sponsor an opportunity to respond to a new set of requests for additional information.

[38]Prior to May 2013, FDA did not have a formal mechanism to track internal appeals of significant decisions and, accordingly, does not have a comprehensive list of such appeals of 510(k) and PMA decisions. However, the agency was able to identify 141 additional appeals—not limited to significant decisions and not a comprehensive list—involving 510(k) and PMA submissions that occurred from about 2005 through 2012 by reviewing other records.

- In an appeal related to a PMA review, the sponsor contended that FDA's not approvable decision reflected an inconsistent and erroneous interpretation of the clinical data supporting the safety and effectiveness of the subject device, and that the data it had provided was sufficient for FDA to reach an approved decision. The sponsor further contended that the review staff failed to utilize the principles outlined in FDA guidance. The review authority upheld FDA's initial decision and determined there was not sufficient valid scientific evidence to demonstrate a reasonable assurance that the subject device was safe and effective under the proposed conditions of use.

The Medical Device Dispute Resolution Panel, which provides another avenue to resolve disagreements between sponsors and the agency, has also addressed issues related to the least burdensome requirements. Since the panel was created following FDAMA in 1997, medical device sponsors have requested that FDA resolve three disagreements through this avenue, each related to PMAs. Although not tracked by FDA, at our request, officials reviewed the records and found that one of the three disputes was related to the least burdensome requirements. Specifically, for a September 2001 dispute, FDA officials said the sponsor requested the panel after FDA initially found that the data from the clinical study submitted by the sponsor did not sufficiently support effectiveness. After reviewing evidence from the applicant and from FDA, the dispute resolution panel determined that the sponsor had provided sufficient evidence to prove effectiveness, and the device was ultimately approved.

FDA Offered Some Training on the Least Burdensome Requirements, and Evaluates its Training for Effectiveness

FDA Offered Some Early Least Burdensome Training at Limited Times, and Has Incorporated Related Information in Broader Training

FDA officials indicated that training specific to the least burdensome requirements was held in the years following the enactment of FDAMA in 1997. FDA was unable to provide records of that training, including its content. However, officials told us that the training was specific to the least burdensome requirements and offered from 1997 through 1999. FDA officials said the agency offered other presentations in subsequent years that they said covered similar least burdensome topics. For

example, the agency provided slides from a presentation created in 2000 that provided an overview of FDA's implementation of the requirements.

Although FDA officials told us this least burdensome specific training was not offered after 1999, they identified various other trainings that they said incorporated the least burdensome concept. For example, a 2005 presentation on clinical trial design has multiple slides on least burdensome requirements, and specifically states that a course objective is to "understand how least burdensome principles apply." Least burdensome requirements are also mentioned in other training materials where they may not be the focus—for example one slide of a presentation on biomarkers included a mention of least burdensome requirements. Officials also identified the training program for new reviewers that FDA implemented in 2011 as a source of training on least burdensome principles. Specifically, the Reviewer Certification Program is a training curriculum that FDA has required most new device reviewers to complete since 2011. The training curriculum covers a wide variety of courses on topics related to a reviewer's responsibilities.[39] While none of these courses is specific to the least burdensome requirements, there are courses covering related topics. For example, there is one course on technical writing that includes FDA's guidance on developing deficiencies with least burdensome principles. Five other courses on different topics mention either the least burdensome requirements or related principles, such as a course on FDA's legislative history that included a slide identifying the least burdensome statutory provisions as an element of FDAMA, though the slide did not explain the least burdensome requirements or provide additional context. Of the 490 staff assigned to review PMAs and 510(k)s, FDA indicated that as of the end of calendar year 2016, 335 had completed the Reviewer Certification Program, 150 started working on premarket submissions prior to the beginning of 2011, and the remaining 5 individuals did not complete the training for varying reasons.[40]

[39]In the materials that FDA provided for the Reviewer Certification Program, there were 18 separate presentations.

[40]According to FDA, 8 of the 150 reviewers who started working on premarket submissions prior to the beginning of 2011 later completed the training. According to FDA, reasons that reviewers starting after 2011 did not complete the training include that they were short-term employees such as fellows or visiting scientists, passed initial testing and were not required to take the complete reviewer certification coursework, or were not required to take the reviewer certification program, as a decision based on general management discretion.

In response to the 21st Century Cures Act, enacted in December 2016, FDA is providing mandatory online training specific to the least burdensome requirements. FDA indicated that the training focuses on key behaviors that reflect the least burdensome approaches as documented in updated guidance that FDA issued in September 2017. FDA officials told us that, as of October 31, 2017, 91 percent of CDRH staff had received the new least burdensome specific training. In addition to the online training, FDA plans other activities, such as follow-up office-level briefings to address questions or concerns and an introductory podcast from the CDRH director. In addition to providing this training to current employees, FDA plans to incorporate least burdensome requirement training into new employee orientation and the Reviewer Certification Program, and plans to include ongoing support and promotion of least burdensome principles through a center working group on the least burdensome requirements. In addition to course-based training, FDA officials told us that least burdensome concepts are conveyed to reviewers through mentoring. Officials explained that much of the training on the least burdensome requirements occurs through mentoring and conversations with supervisors, and that those encounters are not documented.

FDA Is Implementing Evaluations of All Training Courses for Medical Device Review Staff, including Courses that Address the Least Burdensome Requirements

While FDA has not had processes in place to evaluate its medical device training, it is implementing such processes for all training, including courses related to the least burdensome requirements. In its June 2014 report, the contractor performing the independent evaluation noted that CDRH did not have mechanisms in place to measure the quality and effectiveness of its training programs.[41] The report noted that FDA should identify metrics and incorporate methods to better assess review process training satisfaction, learning, and staff behavior changes. FDA officials explained that while they had customer reaction evaluations for trainings for at least 24 years, they started evaluating training participant learning with the Reviewer Certification Program starting in 2010.

[41]Booz Allen Hamilton, *Independent Assessment of FDA Device Review Process Management, Deliverable 10: Final Report on Findings and Recommendations,* a report prepared at the request of the Food and Drug Administration, June 11, 2014.

FDA is in the process of implementing a training evaluation model, which includes various levels of evaluation, from assessing participant response to the training to evaluating its impact on the agency.[42] As of 2017, FDA reported it was evaluating training programs to determine participant learning and preparing to evaluate whether that learning changed participant behavior. Officials told us they anticipate beginning to conduct evaluations that assess agency impact in fiscal year 2018, and they plan to have the model completely implemented for all trainings by fiscal year 2020. FDA currently evaluates its Reviewer Certification Program to determine participant learning, and though the least burdensome requirements are not specifically addressed in the Reviewer Certification Program evaluation materials FDA provided to us, they did include questions on topics related to least burdensome requirements.

In addition to its current training evaluation plan, FDA is also required by the 21st Century Cures Act to conduct an audit of the training and its effectiveness in implementing the least burdensome requirements.[43] Specifically, the training audit is to be conducted by the ombudsman responsible for premarket reviews, identified by FDA as the CDRH Ombudsman.[44] According to a draft plan, FDA plans to conduct training evaluations, a process review of 510(k) and PMA documentation to assess reviewer compliance with FDA procedures, and seek feedback from industry on its experience with the premarket review process and how the least burdensome requirements are applied. Officials indicated that criteria are still under development and that they hoped to have them further developed in the first quarter of 2018, with the authorizing legislation requiring completion of the audit by June 2018, 18 months after enactment of the law.

[42]The model used by FDA is the Kirkpatrick Model, a standard for evaluating the effectiveness of training. It consists of 4 levels: Level 1—Reaction—evaluates how participants respond to the training; Level 2—Learning—measures if they actually learned the material; Level 3—Behavior—considers if they are using what they learned on the job; and Level 4—Results—evaluates if the training positively impacted the organization.

[43]See Pub. L. No. 114-255, § 3058(a), 130 Stat. 1033, 1128-9 (2016) (codified at 21 U.S.C. § 360c(j)(2)).

[44]FDA officials noted that although the CDRH Ombudsman would not typically conduct such an audit, it is statutorily specified to do so. Therefore, officials said that the Ombudsman is coordinating with other center staff to develop the audit plan.

FDA is Taking Steps that May Improve Its Requests for Additional Information Overall, but Has Not Fully Evaluated Its Implementation of the Least Burdensome Requirements

FDA Is Implementing Processes to Improve the Consistency and Clarity of Its Requests for Additional Information during Medical Device Reviews

Some stakeholders and others have raised concerns about the consistency and clarity of FDA's requests for additional information during medical device reviews. For the past 17 years, FDA has required reviewers to only request information that is necessary to make a PMA determination of "reasonable assurance of safety and effectiveness" or a 510(k) determination of "substantial equivalence" in their review of a submission.[45] Representatives of one of the organizations representing the medical device industry noted the high percentages of medical device submissions that involve a letter, and some of their member companies have said that FDA reviewers may request additional information as a result of intellectual curiosity rather than a "need to know." In addition, the independent assessment's 2014 report, funded by FDA as part of MDUFA III, found inconsistent decision-making among FDA review staff throughout various stages of the review process, including additional information requests.[46] While the 2014 report did not address least burdensome requirements explicitly, it examined related processes. For example, according to the report, there was inconsistent decision-making

[45]FDA's past and current guidance recommends that reviewers attempt to resolve minor issues interactively, such as by phone, rather than issuing a formal letter. FDA also recommends that information requested in deficiency letters and AI letters should address the more complicated and complex issues (i.e., major deficiencies) unless minor issues are related to the resolution of substantive issues or remain unresolved at the time the major deficiencies are raised. Under current guidance, additional considerations may also be included but do not require a response. See FDA, *Developing and Responding to Deficiencies in Accordance with the Least Burdensome Provisions*, 2, Nov. 2, 2000 and FDA, *Developing and Responding to Deficiencies in Accordance with the Least Burdensome Provisions Guidance for Industry and Food and Drug Administration Staff*, 2-3, Sept. 29, 2017.

[46]Booz Allen Hamilton, *Independent Assessment of FDA Device Review Process Management, Deliverable 10: Final Report on Findings and Recommendations,* 2014.

among FDA review staff throughout various stages of the review process, including a lack of clarity regarding FDA reviewer thresholds for triggering deficiency letters. The report recommended that FDA develop criteria and establish mechanisms to improve consistency in decision-making throughout the review process.[47]

To address problems identified during the independent assessment, FDA is implementing several initiatives to improve center processes. FDA officials told us that, in anticipation of MDUFA IV, they recognized a need for a dedicated quality management infrastructure. In 2014, FDA established a Quality Management Unit to improve center processes, which they said would include those related to the least burdensome requirements. The unit completed a framework that outlined its vision and mission and established organizational objectives, such as developing a document control system, providing training, and conducting quality assessments, audits, and management reviews.

In addition, FDA officials told us that starting in October 2017, FDA planned to fulfill its MDUFA IV commitments to improve the clarity and consistency of its deficiency letters and AI letters after releasing updated guidance.

- In September 2017, FDA published guidance reflecting the commitments under MDUFA IV that all deficiency letters and AI letters include a statement indicating the specific basis for any cited deficiencies.[48] According to FDA officials, this new approach will help ensure that the letters more consistently ground requests for information in the specific reason that FDA is requesting the information from the sponsor. For example, FDA may cite a law, final rule, or specific scientific issue as the basis for its request, rather than providing a more general statement of the request's relevance. According to industry representatives, in the past, FDA reviewers have, at times, asked for additional information without including justification, and may have requested additional information as a result of intellectual curiosity rather than a "need to know." The

[47]FDA created an action plan in response to this recommendation. The independent assessment's 2016 report included information on the implementation of this action plan, but the initial results of the implementation activities were not measured due to an insufficient observation period.

[48]FDA, *Developing and Responding to Deficiencies in Accordance with the Least Burdensome Provisions*, 2017.

representatives stated that this new policy may better ensure the reviewers apply the least burdensome approach to their review.

- The updated guidance also explains that all deficiency letters and AI letters will undergo supervisory review prior to issuance to ensure that the information requested is relevant to a marketing authorization decision, all four elements of the deficiency are included, deficiencies are prioritized from most to least significant, and each deficiency is appropriate to include in light of the totality of all deficiencies. Officials told us that while supervisory concurrence was previously needed, under the new guidance, supervisors are now expected to review for certain criteria. For example, in the past, supervisors may have considered whether four-part harmony was addressed in each deficiency letter, but under the updated guidance this is now an expected practice. Officials said this will increase the extent to which deficiency letters are consistently constructed.
- In the MDUFA IV commitment letter, FDA agreed to base all deficiency letters and AI letters on a complete review of the submission and include all deficiencies. Therefore, FDA officials told us that any deficiencies identified following that letter would generally be limited to issues raised as a result of new information. For example, if FDA asked for information on bio-compatibility testing, FDA will first review that information, and based on that review may ask for new information. In that instance, the information responding to the initial deficiency is new information. FDA officials said that past letters should also have included all deficiencies, but this may have been done inconsistently.

To further standardize its process for reviewing medical device submissions and developing requests for additional information, FDA is developing and implementing smart templates. FDA officials told us that these templates guide device reviewers through a standardized process for each submission. For example, they help reviewers identify the types of information necessary and include prewritten deficiency letters that have been approved by internal experts. FDA has had a smart template in place for the 510(k) process since 2013, according to FDA reports. FDA indicated that the template is already required for certain offices and divisions within CDRH, and plans for full adoption in the future. FDA officials told us that the agency also developed templates for de novo premarket submissions, which are currently available for voluntary use

and will likely be mandatory in fiscal year 2018.[49] Officials told us they plan to hire a person to develop a template to guide PMA reviews, which will likely take most of 2018. They told us the use of the smart template for PMAS will likely become mandatory for use by all reviewers in 2019. In addition to improving the consistency of deficiency letters, FDA officials said the information generated from the templates could be used to track deficiencies and requests for additional information, as well as provide information on the number and type of deficiencies in the letters. FDA officials told us that the plans for database and back-end analytical capabilities using information from the smart templates were less certain and dependent on available resources, and they pointed out that the information technology infrastructure can present unforeseen challenges.

FDA Has Not Developed Metrics to Evaluate Implementation of the Least Burdensome Requirements, and While a New Audit Process Could Aid Oversight, Its Scope Is Still Unclear

FDA has not established performance metrics that would allow it to evaluate its implementation of the least burdensome provisions. FDA officials told us that the agency does not track concerns related to the least burdensome requirements, such as by examining dispute data to identify those that may be related. According to FDA's 2002 guidance, the agency was in the process of developing tools to be used by both agency staff and its stakeholders to periodically assess the implementation of the least burdensome requirements.[50] The FDA guidance identified a need for additional tools to accurately assess the agency's incorporation of the least burdensome principles into its various regulatory activities and to assess the impact of the least burdensome approach on expediting the development of new medical technologies. Agency officials told us FDA had not developed these tools, but was now in the process of making

[49]An applicant may request a risk-based classification under the *de novo* process for a new device of low to moderate risk, or for which there is no predicate device upon which to base a determination of substantial equivalence. See 21 U.S.C. § 360c(f)(2).

[50]The guidance references two checklists that had already been developed at the time of the guidance. These checklists run through a list of whether or not least burdensome principles have been applied in early collaboration meetings between FDA and the device sponsor. FDA officials confirmed that early collaboration meetings are rarely used in CDRH, as they have been effectively superseded by the pre-submission process. See FDA, *Least Burdensome Provisions: Concept and Principles,* iii, 2002.

other tools available. For example, they cited the development of the smart templates that will guide reviewers as they evaluate medical device submissions and generate deficiency letters. Officials noted that, given the scientific nature of the inquiry, and because least burdensome is a general principle, developing a metric specific to the least burdensome requirements is a challenge. While this can be a challenge, FDA officials have noted that they are attempting to identify surrogate measures that can provide an indication that the reviewer considered the least burdensome requirements when making a request. According to federal standards for internal control, performance metrics are important for management to have relevant, reliable, and timely information available for management decision–making and external reporting purposes.[51] Without such a metric, FDA may be asking medical device sponsors to provide information unnecessarily or in less efficient ways that are not in compliance with the requirement to use the least burdensome approach to medical device reviews.

FDA is in the process of developing an audit program that could provide it with information on its implementation of the least burdensome requirements. FDA has committed to conducting annual quality audits, which will be led by CDRH's Quality Management Unit. Accordingly, FDA plans to identify, with industry input, areas to audit at least once per year. Initially, the agency has agreed to complete an audit of deficiency letters and pre-submissions by the end of fiscal year 2020. As of August 2017, FDA was still planning the deficiency letters audit, and developing its methodology and identifying audit outcomes. FDA officials told us the agency plans to finalize a deficiency letters audit plan by the spring of 2018 and begin data collection by early summer of 2018. Officials explained that the audit will focus on processes—for example, the audit will not examine the scientific content of deficiency letters but will instead focus on whether CDRH has followed existing policies and procedures surrounding deficiency letters. In addition, the Quality Management Unit was still in the process of hiring most of its staff. As of August 2017, FDA officials told us the unit had 6 staff reporting to an Associate Director, and CDRH plans to gradually hire 20 more staff by 2020, starting once MDUFA IV funds are available beginning in October 2017.

In addition to these more specific efforts, FDA also plans to continue its overall evaluation of the medical device review process. The 2016

[51] GAO-14-704G.

independent assessment resulting from MDUFA III broadly evaluated FDA's device review process, and although it mentioned least burdensome requirements only briefly, it addressed a number of related elements, including the quality of the review process and staff training.[52] Under MDUFA IV, FDA committed to another independent assessment in two phases: (1) an evaluation of FDA's implementation of the corrective action plan FDA developed in response to the MDUFA III assessment and (2) an evaluation of FDA's premarket device review program to identify efficiencies that should be realized as a result of the process improvements and investments under MDUFA III and IV, among other things. As with the prior assessment, the new assessment will likely examine processes related to the least burdensome requirements, though the extent to which it will address the requirements is not yet known. Agency officials told us that FDA has committed to hiring a contractor by the end of December 2017.

Conclusions

FDA must balance the need to obtain sufficient data to determine the safety and effectiveness of medical devices under review, with the potential for undue burden and approval delays if unnecessary data is requested. Assuring that the agency uses the least burdensome method to complete its review helps to ensure it is able to make decisions about medical device approval in a timely way. While FDA implemented guidance and training related to the least burdensome requirements following the passage of FDAMA in 1997, it has taken few steps to develop performance metrics to evaluate the extent to which reviewers are using a least burdensome approach when reviewing medical device submissions. Recently, FDA implemented several changes that have the potential to improve its oversight of the least burdensome requirements and the clarity with which reviewers communicate the need for additional information. While planned audits of FDA's medical device review process have the potential to provide the agency with evaluation tools through which to assess performance, these audits are still early in their development and the extent to which they will allow FDA to assess implementation of the least burdensome requirements is unclear. A complete and thorough assessment will be important for the agency to

[52]Booz Allen Hamilton, *Independent Assessment of FDA Device Review Process Management: Deliverable 6: Final Implementation Evaluation Report for the Food and Drug Administration*, 2016.

assure itself and external stakeholders that its reviews adhere to the least burdensome principles and requirements and thus are appropriately balanced.

Recommendation for Executive Action

We are making the following recommendation to FDA:

The Commissioner of FDA should develop performance metrics and use them to evaluate the implementation of the least burdensome requirements, such as during its planned audits of medical device deficiency letters. (Recommendation 1)

Agency Comments

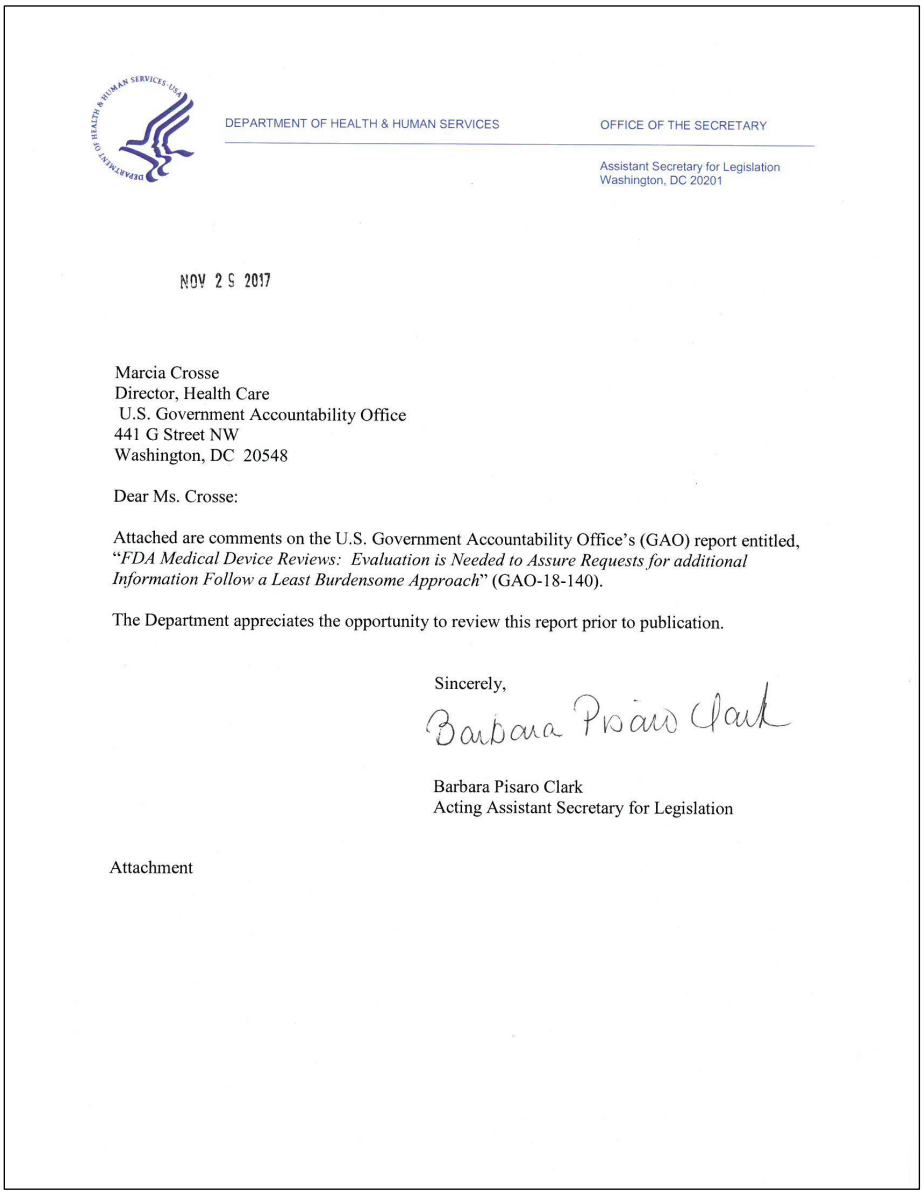
We provided a draft of this report to HHS. HHS concurred with our recommendation and provided written comments, which are reprinted in appendix I. In its written comments, HHS agreed that appropriate implementation of the least burdensome requirements is essential to FDA's evaluation of its PMA and 510(k) medical device submissions, and agreed that it is important for FDA to evaluate how successfully it is implementing the requirements. HHS also reiterated FDA's commitment to the least burdensome principles and provided an overview of its related efforts, several of which were noted in our draft report. HHS noted its concern that our draft report did not sufficiently capture all of FDA's efforts. While HHS cited FDA's efforts related to improving the science underlying its regulatory decisions, which could reduce burden on medical device sponsors, our review focused on the steps involved in FDA's review process. In this regard, HHS concurred with our recommendation that it develop performance metrics and use them to evaluate the implementation of the least burdensome requirements, such as during its planned audits of medical device deficiency letters. In response to this recommendation, HHS indicated that FDA intends to assess how it follows least burdensome requirements as part of these audits. We continue to encourage FDA to develop the evaluation tools necessary to ensure it conducts a complete and thorough assessment of its implementation of the least burdensome requirements. In addition to these general comments, HHS provided technical comments, which we incorporated as appropriate.

As agreed with your office, unless you publicly announce the contents of this report earlier, we plan no further distribution until 30 days from the report date. At that time, we will send copies of this report to the Secretary of Health and Human Services and other interested parties. In addition, the report will be available at no charge on the GAO website at http://www.gao.gov.

If you or your staff have any questions about this report, please contact me at (202) 512-7114 or crossem@gao.gov. Contact points for our Offices of Congressional Relations and Public Affairs may be found on the last page of this report. GAO staff who made major contributions to this report are listed in appendix II.

Marcia Crosse
Director, Health Care

Appendix I: Comments from the Department of Health and Human Services



DEPARTMENT OF HEALTH & HUMAN SERVICES

OFFICE OF THE SECRETARY

Assistant Secretary for Legislation
Washington, DC 20201

NOV 29 2017

Marcia Crosse
Director, Health Care
U.S. Government Accountability Office
441 G Street NW
Washington, DC 20548

Dear Ms. Crosse:

Attached are comments on the U.S. Government Accountability Office's (GAO) report entitled, "*FDA Medical Device Reviews: Evaluation is Needed to Assure Requests for additional Information Follow a Least Burdensome Approach*" (GAO-18-140).

The Department appreciates the opportunity to review this report prior to publication.

Sincerely,

Barbara Pisaro Clark

Barbara Pisaro Clark
Acting Assistant Secretary for Legislation

Attachment

GENERAL COMMENTS OF THE DEPARTMENT OF HEALTH AND HUMAN SERVICES (HHS) ON THE GOVERNMENT ACCOUNTABILITY OFFICE'S DRAFT REPORT ENTITLED - FDA MEDICAL DEVICE REVIEWS: EVALUATION IS NEEDED TO ASSURE REQUESTS FOR ADDITIONAL INFORMATION FOLLOW A LEAST BURDENSOME APPROACH (GAO-18-140)

The U.S. Department of Health and Human Services (HHS) appreciates the opportunity from the Government Accountability Office (GAO) to review and comment on this draft report.

HHS agrees with GAO that appropriate implementation of the least burdensome requirements is essential to the agency's evaluation of device 510(k) and premarket approval (PMA) premarket submissions. HHS also agrees that it is important to evaluate how successfully the Food and Drug Administration (FDA) is implementing the requirements. The agency is concerned, however, that as currently written, the report does not reflect the agency's commitment to the least burdensome principles nor the many changes we have made to our medical device program to apply them.

The least burdensome concept was first introduced in 1997 through the Food and Drug Administration Modernization Act of 1997 (FDAMA). Since the passage of that law, and subsequent acts, the concept has been increasingly integrated into FDA's culture and operations. The agency issued guidance and began to train staff on these principles shortly after FDAMA's enactment. As noted in the report, FDA included standardized language on the least burdensome requirements in its deficiency and Additional Information (AI) letters and guidance documents between 2001 and 2009.

While the initial efforts on least burdensome laid the groundwork, 2010 marked a sea change for FDA as the least burdensome concept would become more deeply and broadly reflected. The agency evaluated all aspects of its device policy and operations to ensure that we were encouraging innovation while preserving patient safety and doing so in the least burdensome way. This effort was buoyed with passage of the Food and Drug Administration Safety and Innovation Act, including the Medical Device User Fees Amendments of 2012 (MDUFA III), which facilitated further integration of least burdensome principles into the agency's work. In fact, FDA stopped including standardized language on least burdensome requirements because template language was used inconsistently and failed to denote the significance of applying the principles, effectively serving as a constraint on the broader application of the least burdensome concept throughout the medical device program. Instead, and more importantly, we focused on incorporating a least burdensome approach into both our general and device-specific policies and recommendations.

FDA's application of the least burdensome principles is reflected in many other recent new policies implemented by FDA. For example, in 2012, FDA implemented a more flexible framework for making benefit-risk determinations in support of PMA approvals and de novo classifications. While also assuring that all applicable regulatory requirements are met, this allowed the agency to reevaluate the extent of evidence necessary to support individual product approvals to further assure we apply the least burdensome principles. One outgrowth of this flexibility is the ability of sponsors of breakthrough devices under a PMA to shift, when appropriate, some premarket data collection to the postmarket setting under our Expedited Access (now Breakthrough Device under the 21st Century Cures Act of 2016) Pathway Program. In 2013, FDA implemented a new policy on early feasibility studies (EFS) to facilitate such

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GENERAL COMMENTS OF THE DEPARTMENT OF HEALTH AND HUMAN SERVICES (HHS) ON THE GOVERNMENT ACCOUNTABILITY OFFICE'S DRAFT REPORT ENTITLED - FDA MEDICAL DEVICE REVIEWS: EVALUATION IS NEEDED TO ASSURE REQUESTS FOR ADDITIONAL INFORMATION FOLLOW A LEAST BURDENSOME APPROACH (GAO-18-140)

studies. As a result, the number of EFS studies approved in the United States increased annually from 33 in 2013 to 47 in 2016 and the number approved annually by FDA has increased from 17 to 40 during the same period. Similar improvements have occurred for other types of clinical trials under new, complementary policies.

FDA's application of the least burdensome principles is reflected in leveraging of new data sources and statistical methods, such as Bayesian statistics. For example, over the past six years FDA has been promoting and expanding the use of "real world data" – data gathered as a part of clinical care, such as in electronic health records and registries – which has resulted in the reduction in time and cost of bringing some new devices to market as well as reducing the time and cost for some sponsors to meet their postmarket study requirements. Based on our preliminary analysis, sponsors of transcatheter aortic valve replacement devices have seen an over 400 percent return on investment for leveraging data from the Transcatheter Valve Therapy Registry that FDA helped establish.

FDA's application of the least burdensome principles is reflected in the development of new regulatory science tools to make device development, assessment, and review safer, faster, and more efficient. For example, our work under the auspices of the Medical Device Innovation Consortium (MDIC), which we co-founded, has led to the creation of new computer models that allow for evidence to support regulatory decisions to be generated in a least burdensome way.

In just the past few years, the results of our application of the least burdensome principles on review issues have been remarkable. With regard to product review, the agency observed a 35 percent reduction in review time between 2009 and 2015 for PMAs, an 11percent reduction in review time between 2010 and 2015 for 510(k)s, a 66 percent reduction in review time between 2009 and 2014 for *de novo* decisions and a reduction of over a year in median time for IDE review times between 2011 and 2015[1] (although the least burdensome requirements only apply to 510(k)s and PMAs, FDA has chosen to apply least burdensome principles more broadly). Moreover, despite a continuous upswing in the percent of 510(k)s and PMAs receiving a deficiency letter between 2002 and 2010, adjustments made pre- and post- MDUFA III saw the relative percentage of deficiency letters decrease from its 2010 peak.[2] Under MDUFA IV, we have already made changes to our deficiency letters, such as including a clear rationale for each deficiency, which reflects the use of least burdensome principles. In addition, our clearance and approval rates for 510(k)s and PMAs, respectively, which had also steadily declined during the first decade of this century, have also been increasing over the past few years. Although the percent or number of deficiency letters issued may not be a true reflection of how well the least burdensome principles have been applied, the decrease in deficiency letters and in review times as well as the increase in clearance/approval rates demonstrate the agency's commitment to applying the least burdensome principles. We are engaging more interactively with sponsors to

[1] "Progress in Achieving Our Vision of Patients First" available at: https://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDRH/CDRHVisionandMission/UCM549979.pdf

[2] Draft: FDA Medical Device Reviews—Evaluation is Needed to Assure Requests for Additional Information Follow a Least Burdensome Approach. See Table 1.

GENERAL COMMENTS OF THE DEPARTMENT OF HEALTH AND HUMAN SERVICES (HHS) ON THE GOVERNMENT ACCOUNTABILITY OFFICE'S DRAFT REPORT ENTITLED - FDA MEDICAL DEVICE REVIEWS: EVALUATION IS NEEDED TO ASSURE REQUESTS FOR ADDITIONAL INFORMATION FOLLOW A LEAST BURDENSOME APPROACH (GAO-18-140)

find creative ways to get to "yes", and streamlining our processes to reduce both the time and cost of bringing safe and effective devices to market.

FDA continues to streamline its processes and remove unnecessary burdens through its continued implementation of a Quality Management System, which it began to implement in 2013. Under MDUFA IV the agency will receive additional resources to further build out its Quality Management capabilities, including to establish an audit function that will assess how well we are applying the least burdensome principles in our premarket program.

The agency is concerned that the report does not sufficiently capture these efforts when describing industry concerns regarding the use of a least burdensome approach in product review. For example, the report notes that 33 out of 63 appeals between 2013 and 2016 reportedly involved concerns over least burdensome requirements. This number, however, isn't contextualized within the total number of applications submitted to the agency during this period: 14,435 510(k)s and 108 original PMAs. The small proportion of reviews triggering least burdensome concerns coupled with the reduction in deficiency letters post 2010, along with shortened review times draws into question the report's seeming suggestion that the agency is failing to implement least burdensome requirements. Limited expressions of dissatisfaction with FDA requests for information when contextualized don't show a pattern of misapplication. The agency has worked hard to properly tailor our requests and while we continue to learn, FDA can point to significant successes.

The successes in the review space have helped to support expansion of the goals of the least burdensome principles into other aspects of FDA's device activities. This has spanned innovative efforts including a major effort to downclassify devices, where appropriate, to reduce the burdens associated with submissions, or to remove those burdens altogether where no longer needed. This has also resulted in efforts to implement risk-based compliance policies. For example, through the implementation of a variety of new policies since 2013 (such as on mobile medical applications, medical device data systems), FDA generally does not oversee devices with dozens of functions in the digital health space (and parallel functions performed by non-digital health devices). FDA's "General Wellness" guidance clarified for industry that we do not intend to examine low risk products that are part of the fitness/wellness industry. The 21st Century Cures Act included provisions that were based on these policies. In 2017, FDA took advantage of a new process under the 21st Century Cures Act to exempt from 510(k) submission over 1,000 different devices. Further, FDA has embraced and led International Harmonization and usage of collaborations with industry to identify areas where regulation is not achieving its intended goal, and may be adding undue burden. For example, FDA, a founding member of the International Medical Device Regulators Forum's led the forum's working group that established the Medical Device Single Audit Program. Under this program, participating countries share their own inspections and rely on surveillance inspections conducted by or on behalf of other participating countries, thereby reducing the number of days participating device companies spend on inspections while allowing government agencies to make better use of their limited resources.

GENERAL COMMENTS OF THE DEPARTMENT OF HEALTH AND HUMAN SERVICES (HHS) ON THE GOVERNMENT ACCOUNTABILITY OFFICE'S DRAFT REPORT ENTITLED - FDA MEDICAL DEVICE REVIEWS: EVALUATION IS NEEDED TO ASSURE REQUESTS FOR ADDITIONAL INFORMATION FOLLOW A LEAST BURDENSOME APPROACH (GAO-18-140)

The resulting impact on public health of FDA's implementation of the least burdensome principles has been significant. For example, as a result of these new and changed policies and processes, we have seen an annual increase in the number of innovative devices approved by FDA from 24 at the end of calendar year 2009 to 91 at the end of calendar year 2016; the highest approval number since the start of the Medical Device User Fee Program in fiscal year 2003. By applying the least burdensome concept in day-to-day practice, we are now seeing high quality, safe and effective devices of public health importance approved in the U.S. in 2016 as the first commercial market, meaning that U.S. patients now have early access to critically important technologies, such as the first "artificial pancreas".

These efforts were further developed under the 21st Century Cures Act, which expanded the application of the least burdensome principles to deficiency letters, required a discussion in FDA summaries of significant decisions of how the agency applied the least burdensome requirements, and required training of all staff involved in the premarket review program. The agency welcomed this mandate, and in fact, has already gone far beyond this obligation. For example, FDA has significantly broadened the scope of what the least burdensome concept entails, expanding its application to all aspects of the Total Product Life Cycle, not just select premarket activities. FDA has further required that all CDRH employees receive training on the least burdensome principles because we believe it is both foundational to our work and it is simply a good government practice. FDA intends to provide the public with these broadened concepts on which its employees have now been trained through the issuance of draft guidance in the coming months.

In sum, while the agency does not disagree with the overall recommendation presented below we would ask that GAO consider providing further context to the report. The least burdensome concept is infused throughout the agency's device work and we would ask that GAO consider more fully reflecting that commitment.

Recommendation 1
The Commissioner of FDA should develop performance metrics and use them to evaluate the implementation of the least burdensome requirements, such as during its planned audits of medical device deficiency letters.

HHS Response
HHS concurs with GAO's recommendation.

FDA intends to assess how we follow least burdensome requirements, including providing an audit of training on least burdensome requirements as provided for in the 21st Century Cures Act, and a broader audit pertaining to premarket review as provided for in the MDUFA IV Commitment Letter.

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Appendix II: GAO Contact and Staff Acknowledgments

GAO Contact

Marcia Crosse (202) 512-7114 or crossem@gao.gov

Staff Acknowledgments

In addition to the contact above, William Hadley (Assistant Director), Matthew Byer (Analyst-in-Charge), Luke Baron, and William Garrard made key contributions to this report. Also contributing were Sam Amrhein and Jennifer Rudisill.

Appendix III: Accessible Data

Data Tables

Data Table for Figure 1: Original Medical Device Premarket Applications Approved by FDA, 2001 to 2016

Fiscal year	Applications approved	Applications other than approved	Applications pending final decision
2001	51	16	0
2002	34	7	0
2003	35	8	0
2004	43	10	0
2005	38	9	0
2006	33	6	0
2007	24	11	0
2008	21	9	0
2009	18	14	0
2010	32	11	0
2011	39	4	0
2012	21	2	1
2013	26	2	1
2014	25	3	0
2015	35	1	6
2016	31	0	24

Data Table for Figure 2: 510(k) Medical Device Notifications Cleared by FDA, 2001 to 2016

Fiscal year	Notifications cleared	Notifications other than cleared	Notification pending final decision
2001	3,551	678	0
2002	3,589	712	0
2003	3,623	572	0
2004	3,189	396	0
2005	3,213	414	0
2006	3,303	529	0
2007	3,052	582	0
2008	3,111	708	0
2009	3,172	907	1
2010	2,894	958	0
2011	3,037	768	0

Fiscal year	Notifications cleared	Notifications other than cleared	Notification pending final decision
2012	3,179	804	0
2013	3,203	663	0
2014	3,057	553	0
2015	3,039	529	2
2016	2,816	519	116

Agency Comment Letter

Text of Appendix I: Comments from the Department of Health and Human Services

Page 1

Marcia Crosse Director, Health Care

U.S. Government Accountability Office 441 G Street NW

Washington, DC 20548 Dear Ms. Crosse:

Attached are comments on the U.S. Government Accountability Office's (GAO) report entitled, "FDA Medical Device Reviews: Evaluation is Needed to Assure Requests for additional Information Follow a Least Burdensome Approach" (GAO-18-140).

The Department appreciates the opportunity to review this report prior to publication.

Sincerely,

Barbara Pisaro Clark

Acting Assistant Secretary for Legislation

Attachment

Page 2

The U.S. Department of Health and Human Services (HHS) appreciates the opportunity from the Government Accountability Office (GAO) to review and comment on this draft report.

HHS agrees with GAO that appropriate implementation of the least burdensome requirements is essential to the agency' s evaluation of device 510(k) and premarket approval (PMA) premarket submissions. HHS also agrees that it is important to evaluate how successfully the Food and Drug Administration (FDA) is implementing the requirements. The agency is concerned, however, that as currently written, the report does not reflect the agency's commitment to the least burdensome principles nor the many changes we have made to our medical device program to apply them.

The least burdensome concept was first introduced in 1997 through the Food and Drug Administration Modernization Act of 1997 (FDAMA). Since the passage of that law, and subsequent acts, the concept has been increasingly integrated into FDA's culture and operations. The agency issued guidance and began to train staff on these principles shortly after FDAMA's enactment. As noted in the report, FDA included standardized language on the least burdensome requirements in its deficiency and Additional Information (AI) letters and guidance documents between 2001 and 2009.

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