The Least Burdensome Provisions: Concept and Principles

Draft Guidance for Industry and Food and Drug Administration Staff

DRAFT GUIDANCE

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When final, this guidance will supersede "The Least Burdensome Provisions of the FDA Modernization Act of 1997: Concept and Principles," issued on October 4, 2002.

U.S. FOOD & DRUG ADMINISTRATION

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health
Center for Biologics Evaluation and Research

Preface

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Draft Guidance for Industry and Food and Drug Administration Staff

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff or Office responsible for this guidance as listed on the title page.

I. Introduction

The Food and Drug Administration (FDA) is committed to helping patients gain more timely access to new medical devices and to maintaining continued access to existing medical devices that are high quality, safe, and effective, by expediting their development, assessment, review, and surveillance, consistent with the Agency's statutory mission to protect and promote the public health.[1] By streamlining regulatory processes and removing or reducing unnecessary burdens associated with FDA regulatory activities, patients can have earlier and continued access to beneficial products.

Since the FDA Modernization Act of 1997 (FDAMA), Congress has directed FDA to take a least burdensome approach to medical device premarket evaluation in a manner that eliminates unnecessary burdens that may delay the marketing of beneficial new products, while maintaining the statutory requirements for clearance and approval. This draft guidance is intended to accurately reflect Congress' intent by describing the guiding principles and recommended approach for FDA staff and industry to facilitate consistent application of least burdensome principles.

We define "least burdensome" to be **the minimum amount of information necessary to adequately address a regulatory question or issue through the most efficient manner at the**

[1] Section 1003 of the Federal Food, Drug, and Cosmetic Act (FD&C Act).

right time. This concept applies to all products that meet the statutory definition of a device and throughout the total product lifecycle (premarket and postmarket).[2]

FDA's guidance documents, including this draft guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidance means that something is suggested or recommended, but not required. Throughout this guidance document, the terms *we*, *us* and *our* refer to FDA staff from the Center for Devices and Radiological Health (CDRH) or the Center for Biologics Evaluation and Research (CBER) involved in device regulation.

II. Background

Congress first added least burdensome provisions to the Federal Food, Drug, and Cosmetic Act (FD&C Act) under FDAMA (Public Law 105-115). Congress enacted additional least burdensome provisions to the FD&C Act through the FDA Safety and Innovation Act (Public Law 112-144) (FDASIA) and the 21st Century Cures Act (Public Law 114-255) (Cures Act). The least burdensome statutory provisions currently state:

- "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."[3]

- "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 a 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."[4]

- In requesting additional information with respect to a premarket approval application (PMA), "the Secretary shall consider the least burdensome appropriate means necessary to demonstrate a reasonable assurance of device safety and effectiveness."[5]

- "[T]he Secretary shall consider the role of postmarket information in determining the least burdensome means of demonstrating a reasonable assurance of device safety and

[2] Section 201(h) of the FD&C Act.
[3] Section 513(i)(1)(D)(i) of the FD&C Act.
[4] Section 513(a)(3)(D)(ii) of the FD&C Act.
[5] Section 515(c)(5)(A) of the FD&C Act.

effectiveness."[6]

- The term "necessary" in the least burdensome provisions means the "minimum required information" that would support a determination of substantial equivalence or a reasonable assurance of device safety and effectiveness.[7]

- The least burdensome provisions do not change the standards for premarket approval or substantial equivalence.[8]

FDA issued least burdensome guidance documents after the enactment of FDAMA. "Suggested Format for Developing and Responding to Deficiencies in Accordance with the Least Burdensome Provisions of FDAMA" ("Deficiencies Guidance") was issued on November 2, 2000. In that guidance document, FDA recommended that its staff use a specific format for requests for additional information needed to make a decision on a medical device marketing submission (often called "deficiencies" or "deficiency letters") to be in accordance with least burdensome principles. This format was intended to directly connect FDA requests to applicable statutory and regulatory criteria for a decision and optimize the time and effort of both industry and FDA. That guidance document also included a recommended format for industry responses to FDA deficiencies.

With the enactment of the Medical Device User Fee Amendments of 2017 (Public Law 115-52, §§ 201-210) (MDUFA IV), FDA committed to updating the Deficiencies Guidance. "Developing and Responding to Deficiencies in Accordance with the Least Burdensome Provisions" (https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm073680.pdf) was issued on September 29, 2017. The Deficiencies Guidance was updated to recommend that all deficiency letters include a statement regarding the basis for each deficiency and provides details regarding supervisory review, major/minor deficiencies, additional considerations, and prioritization of deficiencies.

"The Least Burdensome Provisions of the FDA Modernization Act of 1997: Concept and Principles" was issued on October 4, 2002 ("2002 Least Burdensome Guidance"). The guidance stated that, while the least burdensome provisions from FDAMA applied to PMA and 510(k) submissions, FDA believed that least burdensome principles should be implemented for all premarket regulatory activities. The document also defined the term "least burdensome" and included suggested approaches for industry and FDA staff to use least burdensome principles in PMA and 510(k) review, including focusing on the statutory and regulatory criteria for marketing authorization. The guidance also described general applications of least burdensome approaches to activities such as postmarket controls, and recommendations for how the Agency should communicate requests for additional information to industry.

[6] Section 515(c)(5)(C) of the FD&C Act.
[7] Sections 513(a)(3)(D)(iii), 513(i)(1)(D)(ii), and 515(c)(5)(B) of the FD&C Act.
[8] Sections 513(a)(3)(D)(iv), 513(i)(1)(D)(iii), and 515(c)(5)(D) of the FD&C Act.

This guidance document, when finalized, will replace the 2002 Least Burdensome Guidance. The statutory updates in FDASIA and the Cures Act clarified the original least burdensome provisions and further recognized the role of postmarket activities as they relate to premarket decisions. FDA believes, as a matter of policy, that least burdensome principles should be consistently and widely applied to all activities in the premarket and postmarket settings to remove or reduce unnecessary burdens so that patients can have earlier and continued access to high quality, safe, and effective devices, and the Agency is applying tools in our implementation of these principles, such as regular training of all Center employees on least burdensome principles. This draft guidance, therefore, reflects FDA's belief that least burdensome principles should be applied throughout the medical device total product lifecycle. The least burdensome concept remains the same in that the principles are based on sound science, the intent of the law, the use of alternative approaches, and the efficient use of resources to effectively address regulatory issues. We have provided contemporary examples for both premarket and postmarket settings to demonstrate approaches that FDA and industry can take to ensure that least burdensome principles are implemented for all device-related applications and interactions with FDA.

III. Scope

The least burdensome concept and this guidance apply to all products that meet the statutory definition of a device.[9] The policy in this guidance applies to all activities (including premarket and postmarket actions) pertaining to the regulation of medical devices. The policy in this guidance applies, but is not limited, to:

- Premarket submissions, including PMAs, premarket notifications (510(k)s), De Novo requests, humanitarian device exemption applications, and investigational device exemption applications
- Additional Information and Major Deficiency Letters
- Q-Submissions
- Informal or interactive inquiries regarding device development
- Panel review and recommendations
- Postmarket surveillance and post-approval studies
- Reclassifications and exemptions

[9] Section 201(h) of the FD&C Act.

- Guidance documents and their application
- Compliance-related interactions
- Regulation development

IV. Guiding Principles

FDA defines least burdensome to be the minimum amount of information necessary to adequately address a regulatory question or issue through the most efficient manner at the right time (e.g., need to know versus nice to know). Our least burdensome principles do not change the applicable regulatory standards, such as the device approval or clearance standards, nor the applicable requirements, including premarket submission content requirements and the requirement for valid scientific evidence.[10]

FDA intends to, and industry should, apply the following guiding principles when taking a least burdensome approach to a particular question or issue at any point in the total product lifecycle:

1. FDA intends to request the minimum information necessary to adequately address the regulatory question or issue at hand.

2. Industry should submit material, including premarket submissions, to FDA that are least burdensome for FDA to review.
    - Industry should submit well-organized, clear, and concise information.

3. FDA intends to use the most efficient means to resolve regulatory questions and issues.
    - FDA intends to use all reasonable measures to streamline processes and policies, as well as render regulatory decisions within appropriate timeframes, such as MDUFA performance goals.
    - FDA intends to routinely use interactive approaches, whenever possible, to resolve questions and issues.
    - FDA intends to, and industry should, use tailored approaches that have been adapted to individual circumstances and needs to address regulatory questions and issues.
    - FDA intends to take appropriate consideration of the time and resource implications of its requests.

4. The right information should be provided at the right time (e.g., just-in-time data collection) to address the right questions.

[10] Sections 513(i) and 515 of the FD&C Act and 21 CFR Part 807 Subpart E, Parts 812 and 814, and 860.7(c).

- FDA intends to, and industry should, consider the use of postmarket data collection to reduce premarket data collection whenever appropriate and feasible.

5. Regulatory approaches should be designed to fit the technology, taking into account its unique innovation cycles, evidence generation needs, and timely patient access.

6. FDA intends to leverage data from other countries and decisions by, or on behalf of, other national medical device regulatory authorities to the extent appropriate and feasible.

7. FDA intends to apply least burdensome principles in international medical device convergence and harmonization efforts.

Providing excellent customer service is critical to successfully applying least burdensome principles. FDA strives for clear and concise communication of its requests, expectations, processes, policies, and decisions, as well as the rationale behind them.

Industry can help us apply least burdensome principles by providing FDA with clear and concise requests, premarket submissions, and responses, along with their rationales. Excellent customer service and open lines of communication between FDA and its customers will help to provide regulatory outcomes that best serve patients.

V. Applications of Least Burdensome Principles

This section provides numerous examples intended to represent the least burdensome concept and implementation of least burdensome guiding principles as applied to medical device regulation. This includes examples of using less burdensome sources of clinical data, using nonclinical data, accepting alternative approaches, reducing the burden of traditional clinical studies, using benefit-risk assessments, streamlining processes and reducing administrative burden, engaging in smart regulation, participating in global harmonization, and balancing premarket and postmarket information needs.

While some examples may only be applicable to FDA as a regulatory authority, implementation of the least burdensome principles is a shared responsibility between FDA and industry.

These examples are provided for illustration purposes and are not intended to be an exhaustive list. The examples are grouped by the elements of the least burdensome definition, although some examples could reasonably be included under multiple categories.

A. The minimum information necessary

(1) Less burdensome sources of clinical data

Reasonable assurance of safety and effectiveness of a device is determined on the basis of valid scientific evidence.[11] The evidence required may vary according to the characteristics of the device, its conditions of use, and the extent of experience with its use, among other factors.[12] Alternative sources of clinical data should be considered when appropriate, and, in many cases, may be the least burdensome means for assessing device safety and effectiveness and for other regulatory decision-making. Alternative sources of data may include peer-reviewed literature, outside the U.S. (OUS) data, real-world evidence (RWE), and well-documented case histories. These alternative sources of data should be considered by FDA staff and industry when determining the least burdensome approach to a regulatory requirement or decision. Isolated case reports, random experience, reports lacking sufficient details to permit scientific evaluation, and unsubstantiated opinions are not regarded as valid scientific evidence.[13] Adverse event reports, although not generally considered valid scientific evidence, may be considered as part of a benefit-risk assessment.

Leveraging existing data

The use of existing data to inform regulatory decisions can be a scientifically valid application of the least burdensome principles. When available, appropriate, and relevant to the specific device or regulatory issue at hand, peer-reviewed literature, registry data, and OUS data may be used in lieu of, or to supplement, other data. For example, FDA approved a humanitarian device exemption (HDE) application to treat pediatric esophageal atresia based on a combination of published literature and well-documented compassionate use cases.[14]

Under appropriate circumstances, FDA and applicants may also leverage information contained in a previously filed PMA, including information from clinical or preclinical tests or studies that demonstrate a reasonable assurance of the safety and effectiveness of a device, but excluding descriptions of methods of manufacture, product composition, and other trade secrets. According to the "six-year rule,"[15] while excluding trade secrets, FDA may use safety and effectiveness data from clinical or preclinical tests or studies, six years after PMA approval, in order to approve another applicant's device, establish a performance standard or special control, or classify or reclassify another device under section 513 of the FD&C Act. The Agency decided to apply the six-year rule only to data in PMAs approved after November 28, 1990, the date of enactment of the Safe Medical Devices Act (Public Law 101-629) (SMDA). For example, FDA used the six-year rule upon our own initiative to support the reclassification of stair-climbing wheelchairs from Class III to Class II with the establishment of special controls.[16] For more information on the six-year rule, see the FDA guidance document "Guidance on Section 216 of the Food and Drug Administration Modernization Act of 1997"

[11] 21 CFR 860.7(c)(1).
[12] 21 CFR 860.7(c)(2).
[13] 21 CFR 860.7(c)(2).
[14] Summary of Safety and Probable Benefit available at: https://www.accessdata.fda.gov/cdrh_docs/pdf15/H150003B.pdf.
[15] Section 520(h)(4) of the FD&C Act.
[16] The final reclassification order was issued on April 14, 2014 (79 FR 20779).

(https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm073709.pdf).

The extrapolation of existing clinical data from a studied patient population into a new pediatric patient population should be considered when endpoints present in the existing data source are relevant, there are no differences between adult and pediatric use that could impact safety and effectiveness, and the quality of data is sufficient. For more information on when and how to extrapolate adult data for pediatric populations, see the FDA guidance document "Leveraging Existing Clinical Data for Extrapolation to Pediatric Uses of Medical Devices" (https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-meddev-gen/documents/document/ucm444591.pdf).

Real-world evidence (RWE)

Real-World Data (RWD) are data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources. RWE is the clinical evidence regarding the usage and potential benefits or risks of a medical product derived from analysis of RWD. RWD may originate from electronic health records (EHRs), registries, and medical administrative claims data. For more information about RWE, see the FDA guidance document "Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices" (https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-meddev-gen/documents/document/ucm513027.pdf).

FDA and industry are using RWD sources to address both premarket and postmarket issues. FDA approved a PMA for a permanent pacemaker electrode using clinical data captured though a remote monitoring system in a prospective registry.[17] Several registries initially designed for postmarket surveillance have been used to support expanded indications for devices such as ventricular support devices, vaginal mesh, and transcatheter valves. Finally, FDA and industry leveraged RWE generated from a registry to support expanded indications for use for a cryosurgical tool intended for benign and malignant lesion ablation.[18]

(2) Use of nonclinical data

Nonclinical data should also be considered as an alternative data source. In some cases, this may include the use of benchtop models, nonclinical literature, use of tissue phantoms, or computer modeling and simulations. Especially in situations where testing modalities are representative or predictive of clinical performance, FDA frequently relies upon nonclinical testing in lieu of or to supplement clinical data. For example, FDA has approved magnetic resonance (MR) conditional labeling for pacemakers, cardiac resynchronization therapy devices, and implantable cardioverter defibrillators based, in part, on validated computer modeling. FDA has also accepted cadaver images in lieu of imaging from live subjects for certain imaging indications such as extremity imaging.

[17] Summary of Safety and Effectiveness Data available at: https://www.accessdata.fda.gov/cdrh_docs/pdf12/P120017b.pdf.

[18] 510(k) summary available at: https://www.accessdata.fda.gov/cdrh_docs/pdf17/K171626.pdf.

While clinical data may sometimes be necessary to meet a regulatory requirement, nonclinical data should be considered as a replacement for clinical data, when appropriate. The use of descriptive information, *in vitro* studies, computer modeling and simulations, and/or animal performance data that could be responsive to an outstanding regulatory question should be considered before requesting clinical data.

Bottom-up approach to data requests

Data requests from FDA should follow a stepwise analytical process to ensure that each request reflects the least burdensome approach. This logic has been used for 510(k) submissions to ensure application of least burdensome principles. FDA should first consider whether descriptive information is sufficient. While few 510(k) submissions rely solely on descriptive information, FDA and industry should consider this approach. For example, dimensional analysis and materials comparisons have been used to establish substantial equivalence for orthopedic bone plate and screw 510(k) submissions.

When descriptive information is not sufficient, FDA and industry should then consider whether nonclinical performance testing or analytical studies using clinical samples could address the issue. Nonclinical animal and/or biocompatibility studies are typically requested when other forms of nonclinical bench performance testing are not sufficient to demonstrate substantial equivalence. When analytical or nonclinical bench testing, or nonclinical animal testing and/or biocompatibility studies are insufficient, FDA may request clinical performance data. For more information about how FDA has used this process in 510(k) submissions, see the FDA guidance document "The 510(k) Program: Evaluating Substantial Equivalence in Premarket Notifications [510(k)]" (https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM284443).

Use of nonclinical bench performance testing

Bench performance testing should be considered to address preclinical or clinical endpoints, when appropriate. This may include bench models for anatomy, such as evaluating tortuous paths for catheters used across many clinical applications. The use of tissue phantoms has also increased for evaluating the magnetic resonance imaging compatibility of implants and tissue effects from high intensity therapeutic ultrasound. Bench performance testing may not be an appropriate surrogate when the methods do not correspond with clinically-relevant scenarios.

Computer modeling and simulations (CM&S)

CM&S should be used to support medical device safety and effectiveness as alternatives to traditional benchtop or animal performance testing in appropriate circumstances. For example, CM&S has been used to predict mechanical properties for cardiovascular and orthopedic devices under simulated loading conditions. Additionally, CM&S has been used to estimate the radiofrequency energy absorbed by patients undergoing magnetic resonance imaging (MRI) to assess medical device safety. FDA's recommendations regarding the use of CM&S in submissions are included in the FDA guidance document "Reporting of Computational

Modeling Studies in Medical Device Submissions" (https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM381813.pdf).

(3) Acceptance of alternative approaches

Alternative approaches should be considered, when appropriate, to optimize the time and resources of FDA and industry. Both FDA and industry should understand that there are often multiple ways to satisfactorily address a particular regulatory issue. The resolution of the regulatory issue should be based on a discussion about which method is least burdensome, while still satisfactorily addressing the regulatory issue.

Resolution of scientific issues

The acceptance of alternative approaches for the evaluation of scientific issues identified during the premarket review of a novel medical device is a common application of least burdensome principles. FDA and industry should be flexible and open-minded in determining the most efficient mechanism and minimum information necessary to address a specific issue. In some cases, a justification, in lieu of additional data, may be acceptable to address an issue.

A common example of FDA accepting alternative approaches includes the biocompatibility of medical devices. When appropriate, FDA and industry have leveraged OUS clinical data or large animal safety studies to address certain biocompatibility endpoints. Additionally, the use of rationales based on materials properties, chemistry, and processing have been leveraged as alternatives to repeat testing. For example, manufacturers often modify the tips of their vascular catheters and, instead of repeat testing, leverage prior testing conducted on another vascular device for which the same materials and processing methods were used.

Another common example concerns the review of nonclinical testing in regulatory submissions. Through requests for additional information, the Agency may identify one particular method for addressing a scientific issue. When appropriate, FDA should identify when alternative approaches or justifications would resolve the issue under discussion. Common examples include leveraging existing device information such as mechanical testing, software validation, and sterilization validation. For example, FDA often requests additional bench testing results to address differences in technological characteristics for devices with multiple sizes or models to support substantial equivalence determinations. In consultation with the applicant, FDA has accepted alternative testing and scientific justifications in lieu of previously requested testing for certain device types, for which worst-case testing scenarios can be reasonably justified based on size. In other cases, FDA has requested mechanical testing for certain bone plates or screws, but accepted alternative approaches that included detailed engineering analyses to establish substantial equivalence.

Considering alternative labeling

Applicants propose labeling, including indications for use (IFU), in their regulatory applications. If a labeling statement or proposed IFU is not supported by the submitted evidence and would otherwise result in an adverse decision, such as a not substantially equivalent determination for a

510(k), FDA staff and industry should discuss both (1) a labeling statement or an IFU, if any, that can be supported by the information submitted to FDA, and (2) the minimum information that would support the sought-after labeling statement or IFU. The applicant can then choose which avenue they wish to pursue within statutory and MDUFA deadlines.

In other cases, the addition of specific warnings or precautions to the device labeling may provide sufficient risk mitigation to support a favorable decision. For example, FDA has accepted certain risk mitigations through labeling instead of fail-safe and failure alert mechanisms in its review of CLIA Waiver applications for *in vitro* diagnostic devices (IVDs).

B. The most efficient means

(1) Reducing the burden of traditional clinical studies

When clinical data are necessary, FDA and industry should consider the most efficient means of obtaining the evidence necessary to meet the regulatory need or standard. For example, the PMA requirements for a Class III device include providing a reasonable assurance of safety and effectiveness.[19] In many cases, alternatives to randomized controlled studies may be sufficient. In appropriate circumstances, FDA has accepted historical controls, the use of objective performance criteria (OPC), performance goals (PGs), and alternative sources of data, including evidence from registries, claims data, and published literature. For more information about design considerations for clinical studies, see the FDA guidance document "Design Considerations for Pivotal Clinical Investigations for Medical Devices" (https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM373766.pdf).

Historical control groups

The use of historical control groups involves quantitatively comparing the results of use of the device with prior experience derived from the adequately documented natural history of a disease or condition in comparable patients or populations who received no treatment or who followed an established effective regimen (therapeutic, diagnostic, prophylactic).[20] The use of historical control groups may reduce the number of patients enrolled in clinical studies while retaining their strength as well-controlled clinical investigations. FDA and industry have used historical control groups in the evaluation of generic types of devices including, but not limited to, transcatheter aortic valves, hip resurfacing devices, total knee and ankle replacements, neurostimulators, and diagnostic devices using single-arm clinical study designs to assess safety and effectiveness.

Non-comparative clinical outcome studies

Non-comparative clinical outcome studies can include those using OPCs, PGs, observational studies, registries, meta-analysis, and literature summaries. OPC refers to a target value derived

[19] Section 515 of the FD&C Act.
[20] 21 CFR 860.7(f)(1)(iv)(*d*).

from historical data within clinical studies or registries and is used in a pass/fail manner to assess safety and effectiveness endpoints. PG is a numerical value used as a comparison for safety and/or effectiveness endpoints that may be accepted or developed by a professional society, standards development organization, or FDA. The use of single-group studies compared to an OPC or PG can reduce the sample size necessary to support marketing submissions.

In device types where existing data can be leveraged to set OPCs, such as heart valves, clinical studies are then routinely performed using those OPCs. In another case where less data was available, FDA, in consultation with industry and the Obstetrics and Gynecology Devices Advisory Panel, leveraged five PMA approvals with similar control data to establish an OPC for endometrial ablation devices to give applicants the option to conduct a single-arm study.[21] A single arm study can reduce the study size necessary to demonstrate reasonable assurance of safety and effectiveness.

Subject as own control

When possible, FDA and industry should consider when subjects in clinical studies can serve as their own controls to minimize the number of enrolled patients. Cross-over study designs, where each subject receives the treatment and control interventions sequentially in a randomized order, have been used for clinical studies involving many different devices including obesity devices, dermal fillers, and neurostimulators. Paired designs, where a patient serves as his/her own concurrent control, have been used in split-face study designs to assess plastic surgery devices and split-knees designs to assess orthopedic devices. IVD studies have also used patients as their own controls, for example, to assess the long-term performance of colorectal cancer screening tests.

Adaptive study designs

The use of adaptive study designs may reduce resource requirements, decrease time to study completion, and/or increase the chance of study success. For more information, see the FDA guidance document "Adaptive Designs for Medical Device Clinical Studies" (https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM446729.pdf). Adaptive study designs have been used to minimize the number of study subjects for premarket and postmarket studies for neurological and cardiovascular device types.

Use of alternatives to prospective sample collection

Certain circumstances can make prospective patient samples for IVDs impractical, such as the low prevalence of a condition or the rarity of measuring certain concentration levels in a clinical setting. In such cases, alternative approaches to sample collection should be considered, such as the use of banked and retrospective samples, contrived samples, and surrogate samples or biomarkers.

[21] FDA Letter to Global Endometrial Ablation Manufacturers is available at: https://www.fda.gov/downloads/MedicalDevices/ResourcesforYou/Industry/UCM470246.pdf.

(2) Use of benefit-risk assessments

Least burdensome principles are consistent with FDA's approach to weighing benefits and risks in regulatory decision-making. All regulatory processes involve some uncertainty about the benefits and risks of a medical device. Greater uncertainty is appropriate in some circumstances, such as when the probable benefits are high (e.g., a breakthrough device) or the probable risks of the device are low.

Marketing submissions

In determining the safety and effectiveness of a device, FDA considers, among other factors, the probable benefit to health from the use of the device weighed against any probable injury or illness from such use.[22] The extent (probability, magnitude/severity, and duration) of both benefit and risk are considered along with uncertainty, patient-centric metrics and perspective, and a characterization of the disease. A positive decision may be rendered when FDA determines that the probable benefits to health outweigh any probable risks and that the device will provide clinically significant results.[23] For example, despite the occurrence of serious adverse events and death in clinical studies and OUS registries for a mitral valve repair device, FDA determined that there was a narrow patient population with low life expectancy and quality of life for which the probable benefits outweigh the probable risks.[24] This device provided an unmet clinical need for treatment in patients who were not candidates for mitral valve surgery. Taking into account the benefit-risk assessment, FDA determined that the device has a reasonable assurance of safety and effectiveness for this narrow patient population.

For more information about using benefit-risk in PMA and De Novo request decisions, see the FDA guidance document "Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approval and De Novo Classification" (https://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm517504.pdf).

(3) Streamlining processes and reducing administrative burden

Least burdensome principles also apply to streamlining regulatory processes to improve efficiency. FDA has implemented several policies and practices to reduce administrative burden, eliminate potential redundancies, and conserve both FDA and industry resources.

Reducing redundancies

The inclusion of multiple devices or indications within a bundled marketing submission or the use of dual submissions can limit redundant submission and review of regulatory information by FDA and industry. Bundling is appropriate for generic types of devices with scientific and regulatory issues that can be most efficiently addressed during one review. For more information about bundling, see the FDA guidance document "Bundling Multiple Devices or Multiple

[22] 21 CFR 860.7(b)(3).
[23] 21 CFR 860.7(d)-(e).
[24] Summary of Safety and Effectiveness Data available at: https://www.accessdata.fda.gov/cdrh_docs/pdf10/P100009B.pdf.

Indications in a Single Submission" (https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089732.pdf).

The dual 510(k)/CLIA Waiver permits the concurrent review of a 510(k) submission and CLIA Waiver application. FDA and industry work collaboratively to develop comparison and reproducibility study designs to generate one data set that should reduce study-related costs and review time. For more information about the dual 510(k)/CLIA Waiver, see the FDA guidance document "Administrative Procedures for CLIA Categorization" (https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070889.pdf).

Marketing submission efficiencies

Special and Abbreviated 510(k) submissions rely on conformance with design controls and conformity to FDA-recognized voluntary consensus standards. PMA annual reports can be used to summarize design, labeling, and manufacturing changes that do not affect safety and effectiveness.

Medical Device Development Tools (MDDTs)

An MDDT is a method, material, or measurement used to assess the effectiveness, safety, or performance of a medical device. MDDTs are tools that can be qualified and used to streamline device development and regulatory evaluation. The efficient use of MDDTs can reduce development costs and review times after tool qualification. For more information about MDDTs, see the FDA guidance document "Qualification of Medical Device Development Tools" (https://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm374432.pdf).

Medical Device Reporting (MDR)

Reducing the burden of MDRs has been executed through enhancements to existing processes. The Electronic MDR (eMDR) system has been implemented to fast-track the generation, submission, and review of MDRs. The use of eMDR expedites report processing and reduces the data entry burden on industry, FDA, healthcare facilities, and importers. For more information about eMDR, see the FDA guidance document "Questions and Answers about eMDR – Electronic Medical Device Reporting" (https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm179471.pdf).

Alternative summary MDR reporting can be requested by persons and entities that are not exempt from mandatory reporting. FDA may grant an alternative, or full or partial exemption from the MDR regulations.[25] For example, manufacturers may request that reports be submitted quarterly, semiannually, or annually instead of 30 calendar days after becoming aware of the reportable event. Additionally, manufacturers can request that reports only contain a subset of

[25] 21 CFR 803.19.

the data required by the MDR regulations. Registry data used for postmarket surveillance has allowed manufactures to apply for alternative summary reporting where only certain adverse events must be reported to the FDA. In some cases, FDA has allowed manufactures to provide a summary MDR report generated from a specific registry each quarter. For more information about alternative summary and summary MDR reporting, see the FDA guidance documents "Medical Device Reporting – Alternative Summary Reporting (ASR) Program" (https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm072102.pdf) and "Medical Device Reporting for Manufacturers" (https://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm359566.pdf).

(4) Smart regulation

The application of least burdensome principles should include a regular reexamination of the regulatory paradigm for medical devices to ensure that existing regulatory processes are still the most efficient and request the minimum information necessary. As specific medical technologies become better understood from a scientific and clinical perspective, FDA should periodically assess the appropriateness of data requests in premarket submissions, evaluate premarket and postmarket balance, and determine whether devices are candidates for reclassification, as such evaluation may help FDA focus on issues of higher public health concern.

Exemption from 510(k)

Central to reexamination of regulatory processes is the consideration of whether premarket submissions are necessary to reasonably assure a device's safety and effectiveness. In accordance with the FD&C Act, as amended by the Cures Act, FDA published notices exempting numerous Class II and Class I device types from 510(k) requirements.[26] FDA is also required to periodically publish a list of device types for which a 510(k) submission is no longer necessary to provide a reasonable assurance of safety and effectiveness.[27]

(5) Global harmonization

Efforts to advance international harmonization and regulatory convergence should be viewed as applying the least burdensome concept by using the most efficient means to achieve regulatory goals. While U.S. statutes and regulations may not be identical to those of other countries, FDA should align itself with international regulatory authorities whenever practicable and possible.

Reliance on voluntary consensus standards

The development of voluntary consensus standards allows FDA, industry, and other stakeholders to agree upon methods and acceptance criteria that can be used to support the safe and effective use of medical devices. The recognition of standards by FDA can streamline interactions between FDA and industry. When recognized and used by multiple regulatory authorities,

[26] Sections 510(l)(2) and (m)(1) of the FD&C Act. The final exemption notices for Class I and Class II devices were published in the Federal Registers of April 13, 2017 (82 FR 17841) and July 11, 2017 (82 FR 31976), respectively.
[27] Sections 510(l)(2) and (m)(1) of the FD&C Act.

standards can also support global harmonization by creating consistent approaches to medical device evaluation. For more information, see section 514(c) of the FD&C Act and the FDA guidance document "Recognition and Use of Consensus Standards" (https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm077295.pdf).

In the absence of a recognized consensus standard, evaluation of performance data involves the submission and review of complete test protocols and data reports. By providing a declaration of conformity to FDA-recognized standards with explicit testing methods, applicants and FDA do not need to discuss whether test methods are scientifically valid and can focus their resources on reviewing the test data. When consensus standards have both explicit test methods and either performance limits and/or acceptance criteria, a declaration of conformity can potentially replace the submission and review of both the test methods and complete data. FDA accepts declarations of conformity for many generic device types to support regulatory submissions.

International Medical Device Regulators Forum (IMDRF)

FDA's participation on the IMDRF to develop internationally recognized guidance documents, standards, and auditing practices supports regulatory convergence. IMDRF is a voluntary group of international regulatory authorities intended to build on previous work from the Global Harmonization Task Force on Medical Devices (GHTF). This includes the piloting of both the Summary Technical Documentation (STED) format and Regulated Product Submission (RPS) for regulatory submissions. Harmonization of FDA's content requirements for marketing submissions with those of international regulatory authorities can streamline applicant efforts to address a regulatory issue. FDA's participation on IMDRF's work items related to Software as a Medical Device (SaMD) also seeks to harmonize FDA's clinical evaluation of SaMD with those of the international community.

Medical Device Single Audit Program (MDSAP)

MDSAP is a program that applies the least burdensome principles by allowing for one audit to satisfy the requirements of multiple regulatory jurisdictions. The goal is to reduce regulatory burden on industry by minimizing audits with potential redundant requests or disruption of business by different international regulatory authorities.

C. The right time

(1) Balancing premarket and postmarket information needs

Striking the right balance between premarket and postmarket information needs is a key principle of the least burdensome concept. This balance is intended to address obtaining the minimum necessary information at the right time in the total product lifecycle. As discussed in the Background (section II), the FD&C Act requires FDA to consider the role of postmarket information when making a determination of the least burdensome means of demonstrating a

reasonable assurance of safety and effectiveness for PMAs.[28] FDA and industry should consider the appropriate balance between premarket and postmarket information needs for all medical device regulatory issues, when applicable.

Reviewing only some changes

FDA and industry's reliance on the Quality System (QS) Regulation (21 CFR Part 820) is another example of the application of least burdensome principles that supports efficiency. Manufacturers have the ability to make certain design changes to cleared devices and labeling without reporting under section 510(k) of the FD&C Act. For more information, see the FDA guidance documents "Deciding When to Submit a 510(k) for a Change to an Existing Device" (https://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm514771.pdf) and "Deciding When to Submit a 510(k) for a Software Change to an Existing Device" (https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM514737.pdf).

Total product lifecycle approach

FDA should only request information that is necessary to make a given regulatory decision. When requesting information, FDA should assess the right time for obtaining necessary information and determine whether a shift from premarket to postmarket evaluation is appropriate while still reasonably assuring device safety and effectiveness. Reliance on postmarket controls, such as the QS Regulation, post-approval studies (PAS), postmarket surveillance, and MDR, should be considered when determining the suitability for devices for the market. In some cases, FDA has determined that premarket review is not required to reasonably assure a device's safety and effectiveness. For example, some medical devices that are exempt from premarket review rely on the QS Regulation and other postmarket controls to reasonably assure their safety and effectiveness.

In other cases, certain safety and effectiveness questions may be appropriately and efficiently answered in a postmarket setting. For example, long-term safety and effectiveness questions for a leadless pacemaker were addressed through PAS. Analytical studies for long-term outcomes regarding companion diagnostics have also been addressed in a postmarket setting, when appropriate. For more information about FDA's recommended approach to premarket/postmarket balance, see the FDA guidance document "Balancing Premarket and Postmarket Data Collection for Devices Subject to Premarket Approval" (https://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm393994.pdf).

VI. Compliance Policies that Support the Goals of the Least Burdensome Concept

[28] Section 515(c)(5)(C) of the FD&C Act.

The compliance policies below help support the goals of the least burdensome concept by allowing for more efficient and effective use of resources by both FDA and industry.

Enforcement discretion policy

In some cases, FDA has published guidance documents communicating that the Agency does not intend to examine whether certain products comply with premarket review and postmarket regulatory requirements for devices under the FD&C Act and its implementing regulations, including, but not limited to: registration and listing and 510(k) requirements; labeling requirements; current good manufacturing practice requirements as set forth in the QS Regulation; and MDR requirements.[29] Although these guidances do not change or otherwise affect any requirements of the FD&C Act or any applicable regulations, FDA has used this approach for products such as mobile medical applications and general wellness products so that FDA can focus its oversight on those medical devices whose functionality could pose a higher risk to patients. For more information, see the FDA guidance documents "Mobile Medical Applications" (https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM263366) and "General Wellness: Policy for Low Risk Devices" (https://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm429674.pdf).

Medical necessity for marketed devices

FDA recognizes that devices may have benefit even when the devices fail to meet all regulatory requirements. When contemplating exercising enforcement discretion for a violative device, FDA considers the needs of patients and clinicians. In cases when there are no alternative devices, or the risk associated with changing to an alternative is greater than the risk associated with the violative devices, FDA can determine the violative devices to be medically necessary for some situations. For example, FDA may exercise discretion by not taking enforcement action against a violative device, in order to address patient and clinician need. FDA bases this determination on benefit-risk principles and revisits the analysis as new information becomes available.

For more information about using benefit-risk in compliance/enforcement decisions, see the FDA guidance document "Factors to Consider Regarding Benefit-Risk in Medical Device Product Availability, Compliance, and Enforcement Decisions" (https://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm506679.pdf).

VII. Conclusion

When finalized, this draft guidance will reflect the principle that medical device regulation should be least burdensome across the total product lifecycle. FDA intends to request the

[29] 21 CFR Part 807, Part 801 and 809.10, Part 820, and Part 803, respectively.

minimum amount of information necessary to adequately address a regulatory question or issue through the most efficient manner at the right time. Industry should provide information to FDA that is least burdensome for FDA to review. Open lines of communication between FDA and industry will provide regulatory outcomes that best serve patients. Successful application of least burdensome principles will ensure that patients have access to high-quality, safe, and effective medical devices.