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Recommendations for the Use of Clinical Data in Premarket Notification [510(k)] Submissions

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Draft Guidance for Industry and Food and Drug Administration Staff

DRAFT GUIDANCE

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Preface

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Recommendations for the Use of Clinical Data in Premarket Notification [510(k)] Submissions

Draft Guidance for Industry and Food and Drug Administration Staff

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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

As part of FDA's Medical Device Safety Action Plan: Protecting Patients, Promoting Public Health (herein referred to as the "Safety Action Plan"),[1] FDA committed to strengthen and modernize the premarket notification [510(k)] Program. FDA is issuing this guidance to provide our current thinking on the use of clinical data in 510(k) submissions to enhance the predictability, consistency, and transparency of the 510(k) Program. The intent of this guidance is to clarify and provide additional context for situations when clinical data may be necessary to demonstrate substantial equivalence (SE), as initially described in "The 510(k) Program: Evaluating Substantial Equivalence in Premarket Notifications [510(k)]" guidance (herein referred to as the "510(k) Program Guidance").[2]

In that guidance, FDA described the most common scenarios for when clinical data may be necessary in a 510(k) submission. The scenarios are further described in this guidance, and FDA has described another scenario. In addition, FDA is providing additional examples to clarify these concepts, illustrating when clinical data may or may not be needed. Providing clarity and predictability about when clinical data may be necessary to include in a 510(k) submission to demonstrate SE will aid in protecting and promoting public health.

[1] Available at https://www.fda.gov/about-fda/cdrh-reports/medical-device-safety-action-plan-protecting-patients-promoting-public-health.

[2] Available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/510k-program-evaluating-substantial-equivalence-premarket-notifications-510k.

In general, FDA's guidance documents 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 guidances means that something is suggested or recommended, but not required.

II. Background

In April 2018, CDRH issued the Safety Action Plan to communicate CDRH's vision for modernizing measures to improve the safety of medical devices while continuing to create more efficient pathways to bring critical devices to patients. The Safety Action Plan describes efforts underway to enhance our programs to help improve device safety.

In November 2018, FDA announced transformative additional steps to modernize FDA's 510(k) Program to advance the review of the safety and effectiveness of medical devices.[3] In connection with this announcement, FDA also requested public feedback on these steps to continue to modernize the framework for 510(k) review while promoting patient safety and posed other questions that could inform regulatory policy development.[4] One area identified by the public comments where additional clarity and transparency would be helpful was the use of clinical data in 510(k) submissions.

Under section 510(k) of the Federal Food, Drug, and Cosmetic (FD&C) Act, a premarket notification submission (often referred to as a 510(k)) must be submitted to FDA at least 90 days before introducing, or delivering for introduction, a device into interstate commerce for commercial distribution.[5] A 510(k) is required for devices intended for human use, for which a premarket approval application (PMA) is not required, unless the device is exempt from the 510(k) requirements of the FD&C Act and does not exceed the relevant limitations of exemptions in the device classification regulations. Through review of the 510(k), FDA determines whether the "new device"[6] is substantially equivalent[7] (SE) to a predicate device.[8]

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[3] Please see the Statement from then FDA Commissioner Scott Gottlieb, M.D., and Jeff Shuren, M.D., Director of the Center for Devices and Radiological Health, on November 26, 2018, available at https://www.fda.gov/news-events/press-announcements/statement-fda-commissioner-scott-gottlieb-md-and-jeff-shuren-md-director-center-devices-and.

[4] Please see "Modernizing FDA's 510(k) Program; Establishment of a Public Docket; Request for Comments," Docket Number FDA-2018-N-4751, available at https://www.regulations.gov/docket/FDA-2018-N-4751.

[5] Under section 510(k) of the FD&C Act, a 510(k) is required for devices that are not subject to a premarket approval application, unless the device is exempt from the 510(k) requirements of the FD&C Act and does not exceed the limitations of exemptions for each of the device classification regulations (see 21 CFR Parts 862-892). See sections 510(k) and (n) of the FD&C Act (21 U.S.C. §§ 360(k) & (n)).

[6] For purposes of this guidance, a "new device" means a device within the meaning of section 201(h) of the FD&C Act that is not legally marketed. It can be either a completely new device or a modification of a legally marketed device that would require a new 510(k).

[7] The standard for a substantial equivalence determination for a 510(k) submission is set out in section 513(i) of the FD&C Act.

[8] For purposes of an SE determination, a predicate device is (1) a device that was legally marketed prior to May 28, 1976 (preamendments device) and for which a PMA is not required, or (2) a device that has been classified or

For additional information on how FDA evaluates SE in the 510(k) review process, please see the 510(k) Program Guidance.

For FDA to find a new device SE to a predicate device, FDA must first find that the new device and predicate device have the same intended use. FDA must then find that the new device and predicate device have the same technological characteristics, or if they do not, that the different technological characteristics[9] of the new device do not raise different questions of safety and effectiveness and that the new device is as safe and effective as a predicate device.

To determine the safety and effectiveness of a device, FDA also weighs if there is "any probable benefit to health from the use of the device against any probable risk of injury or illness from such use,"[10] among other relevant factors. Under the 510(k) paradigm, the benefit-risk profile of the new device is determined in the context of a comparison to the benefit-risk profile of a predicate device; the benefit-risk profile of a new device with different technological characteristics does not need to be identical to that of its predicate device in order to determine if the new device is as safe and effective as a predicate device. The FDA guidance "Benefit-Risk Factors to Consider When Determining Substantial Equivalence in Premarket Notifications (510(k)) with Different Technological Characteristics"[11] describes considerations for evaluating benefit-risk profile of a device in comparison to a predicate device for purposes of SE determinations.

In many cases, a new device that is subject to 510(k) requirements can demonstrate SE to a predicate device through robust non-clinical safety and performance data, without the need for clinical data, for example, because the intended use and technological characteristics of the new device is the same as, or sufficiently similar to, that of the predicate device. In such circumstance, clinical data would not be necessary to demonstrate SE to a predicate device, and requiring clinical data would be inconsistent with the least burdensome provisions of the FD&C Act.[12] However, for certain devices subject to 510(k) requirements, obtaining clinical data may be necessary to demonstrate that a new device is SE to a predicate device.

As described in the 510(k) Program Guidance, when analytical or non-clinical bench performance testing data or non-clinical animal[13] and/or biocompatibility studies are insufficient,

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reclassified into Class II or I, or (3) a device that has been found to be SE through the 510(k) process. See 21 CFR 807.92(a)(3) and section 513(f)(2) of the FD&C Act.

[9] A predicate device is a legally marketed device. For purposes of an SE determination, "'different technological characteristics' means, with respect to a device being compared to a predicate device, that there is a significant change in the materials, design, energy source, or other features of the device from those of the predicate device." See section 513(i)(l)(B) of the FD&C Act.

[10] See 21 CFR 860.7(b).

[11] Available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/benefit-risk-factors-consider-when-determining-substantial-equivalence-premarket-notifications-510k.

[12] See section 513(i)(1)(D)(ii) of the FD&C Act, and "The Least Burdensome Provisions: Concept and Principles" guidance, available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/least-burdensome-provisions-concept-and-principles.

[13] FDA supports the principles of the "3Rs" to replace, reduce, and/or refine animal use in testing, when feasible. We encourage manufacturers to consult with FDA if they wish to use a non-animal testing method that they believe

or available scientific methods are not acceptable, e.g., the scientific methods are deemed unacceptable because they are not clinically validated or are not supported by a valid scientific rationale, FDA may request clinical performance data to support an SE determination. In such cases when clinical data are necessary, it may include, for example, data comparing the technological characteristics of the new device to the predicate device, data assessing whether a change in the indications for use results in a different intended use,[14] or data supporting the assessment of the benefit-risk profile of a new device to demonstrate that the new device is as safe and effective as a predicate device.

Clinical data provided in support of any marketing submission, including a 510(k) submission, should constitute valid scientific evidence as defined in 21 CFR 860.7(c)(2).[15] Clinical data may include, but are not limited to, results of pre- and post-market clinical investigation(s) of the device (i.e., traditional clinical trials); results of pre- and post-market clinical investigation(s) or other studies reported in the scientific literature of a comparable device; published and/or unpublished reports on clinical experience of either the device in question or a comparable device; and other sources of clinical experience such as registries, adverse event databases, and medical records (e.g., electronic health records, claims).[16] Many of these sources constitute real-world data,[17] and the relevance and reliability of such data should be considered in evaluating whether the data constitutes valid scientific evidence sufficient to support the 510(k) submission. Additionally, when considering whether data collected on a comparable device, such as an earlier version of a device or a similar model of a device, may address certain questions of safety and effectiveness, an adequate justification regarding the applicability of such data should be provided demonstrating why such data would be representative of the new device. In some cases, non-clinical data may also be needed to demonstrate that the devices are comparable and that the clinical data from the comparable device are applicable to the new device. For purposes of this guidance, data obtained from human factors testing is not considered clinical data.

is suitable, adequate, validated, and feasible. We will consider if a proposed alternative method could be assessed for equivalency to an animal test method.

[14] As described in the 510(k) Program Guidance, for purposes of SE, the term "intended use" means the general purpose of the device or its function, and encompasses the indications for use. The term "indications for use" describes the disease or condition that the device will diagnose, treat, prevent, cure, or mitigate, including a description of the patient population for which the device is intended.

[15] 21 CFR 860.7(c)(2) states that "Valid scientific evidence is evidence from well-controlled investigations, partially controlled studies, studies and objective trials without matched controls, well-documented case histories conducted by qualified experts, and reports of significant human experience with a marketed device, from which it can fairly and responsibly be concluded by qualified experts that there is reasonable assurance of the safety and effectiveness of a device under its conditions of use."

[16] These example sources of clinical data are leveraged from the International Medical Device Regulators Forum Document, "Clinical Evidence – Key Definitions and Concepts," available at http://www.imdrf.org/docs/imdrf/final/technical/imdrf-tech-191010-mdce-n55.pdf.

[17] For additional information regarding real world data, refer to FDA's guidance, "Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices," available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/use-real-world-evidence-support-regulatory-decision-making-medical-devices.

III. Scope

This guidance provides recommendations for when clinical data may be needed to demonstrate that a device reviewed under the 510(k) Program is SE to a predicate device. The recommendations in this guidance are consistent with the 510(k) Program Guidance and expand on Section IV.F of that guidance. This guidance also provides additional detail on situations where providing clinical data may be the least burdensome[18] means of demonstrating SE between a new device and a predicate device. FDA developed this guidance to improve the predictability, consistency, and transparency of the 510(k) premarket review process.

This guidance does not describe situations when postmarket collection of clinical data may be appropriate, such as when clinical data are required in a postmarket surveillance study.[19] This guidance, and the concepts discussed herein, are not intended to propose any changes to applicable statutory and regulatory standards, such as how FDA evaluates SE, or the applicable requirements, including 510(k) content requirements and the requirement for valid scientific evidence.[20] This guidance is intended to describe scenarios when clinical data may be necessary and is not intended to supersede applicable regulatory requirements of special controls that outline clinical data requirements for certain device types.

The principles in this guidance are applicable to devices that are subject to 510(k) review by CDRH and CBER; however, this guidance is not intended to supplant existing device-specific guidance. This guidance does not address review issues unique to combination products. For information on combination products, please refer to the Office of Combination Products webpage.[21]

If you have questions about how this guidance and a device-specific guidance apply to a particular issue, we recommend that you consider the general recommendations in this document and discuss specific questions with the appropriate review division associated with your device by submitting a pre-submission. Additional information on the pre-submission program is available in the FDA guidance, "Requests for Feedback and Meetings for Medical Device Submissions: The Q-Submission Program."[22]

[18] See *supra* n. 13.
[19] Section 522 of the FD&C Act. For further information on postmarket surveillance studies, see FDA's guidance, "Postmarket Surveillance Under Section 522 of the Federal Food, Drug, and Cosmetic Act," available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/postmarket-surveillance-under-section-522-federal-food-drug-and-cosmetic-act.
[20] Sections 513(i) and 515 of the FD&C Act, 21 CFR Part 807 Subpart E, and 21 CFR 860.7(c)(2).
[21] Available at https://www.fda.gov/combination-products.
[22] Available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/requests-feedback-and-meetings-medical-device-submissions-q-submission-program.

IV. Appropriate Use of Clinical Data in 510(k) Decision-Making

As described in the 510(k) Program Guidance, clinical data may be used during the 510(k) review process to support an SE determination at multiple points in the decision tree to address the critical questions in the 510(k) Decision-Making Flowchart.[23]

Typically, clinical data is reviewed after FDA finds that the intended use of the new device and the predicate device are the same, and that the devices have different technological characteristics that do not raise different questions of safety and effectiveness.[24] In such cases, clinical data often is used to determine whether the new device is "as safe and effective" as a predicate device. However, clinical data may also be reviewed at other stages of the 510(k) review process. For example, in rare instances, FDA may rely upon clinical data to determine that new[25] or modified indications for use fall within the same intended use as a predicate device.[26] This guidance describes some of the more common scenarios where clinical data may be necessary to determine SE.

V. Scenarios When Clinical Data May be Necessary to Determine Substantial Equivalence

FDA initially described the most common scenarios for when clinical data may be necessary in a 510(k) submission to demonstrate SE and provided illustrative examples in the 510(k) Program Guidance, Section IV.F, "Requests for Performance Data."

In this guidance, FDA provides additional clarity on those scenarios (Scenarios 1 – 3 below), and describes another scenario (Scenario 4 below), to provide broad considerations to be used by industry and FDA to help determine whether clinical data may be necessary to demonstrate that a new device is SE to a predicate device:

1. There are differences between the indications for use of the new device and the predicate device, and clinical data may be needed to determine SE.
2. There are differences between technological characteristics of the new device and the predicate device, and clinical data may be needed to determine SE.
3. SE between the new device and the predicate device cannot be determined by non-clinical testing (analytical, bench, and/or animal).
4. A newly identified or increased risk for the predicate device suggests clinical data may be needed for the new device in order to determine SE.

[23] See 510(k) Program Guidance, Appendix A, Decision Points 1 through 4.
[24] See *id.* at Decision Points 5a and 5b.
[25] As used in this guidance, the term "new" in describing indications for use refers to an indication that is new or differs from that of the predicate device.
[26] See *id.* at Decision Point 2.

The information below provides additional descriptions of each of the scenarios for when clinical data may be necessary to determine SE, as well as illustrative examples. The applicability of these scenarios may be determined based upon current knowledge, understanding, evidence, and experience available for the new device. Following the least burdensome provisions, the need for clinical data may also change as information on the device type is accrued. FDA acknowledges that there may be situations where one or more of these scenarios exist, but clinical data may not be needed depending on the specific circumstances surrounding the particular new device. Accordingly, for each scenario, FDA has provided examples where clinical data may be needed, as well as examples where clinical data are not typically needed, to determine SE. In addition, there may be other scenarios not described herein for which clinical data may be necessary to determine SE. Note, as described in the 510(k) Program Guidance, the examples provided below distinguish between examples that are only applicable to diagnostic devices, including in vitro diagnostics (IVDs), and therapeutic devices. This is because there are significant differences in the types of clinical data that may be needed to determine SE for these two categories of devices.

A. Scenario #1 – Differences in the indications for use

As described in the 510(k) Program Guidance, when the indications for use of a new device and predicate device differ, FDA must evaluate whether the indications for use of the new device fall within the same intended use as that of the predicate device. FDA determines the indications for use of the new device based on the proposed labeling[27] and the indications for use statement in a 510(k). Following review of the proposed labeling and indications for use statement, FDA may rely upon other clinical and/or scientific information submitted with the 510(k) in order to determine if the new device has the same intended use as the predicate device.

The following factors could impact when clinical data may be necessary to include in a 510(k) submission to demonstrate SE when there are differences between the indications for use of the new device and the predicate device, as shown in illustrative examples 1-A, 1-B, 1-C, and 1-D:

- Differences in the patient population
- Differences in the disease
- Differences in the anatomical site, structure, or pathology
- General to specific considerations[28]
- Expansion of the new device's currently-cleared indications for use
- Unknown or different benefit-risk profile for the proposed indications for use

Example 1-A: A certain device typically does not require clinical data to be included in a 510(k) submission. However, if a new device is indicated for use in a higher risk population (e.g.,

[27] Pursuant to section 513(i)(1)(E)(i) of the FD&C Act, the proposed labeling in a 510(k) submission is used to determine a device's intended use. The intended use of a device encompasses the indications for use.

[28] See 21 CFR 807.92(a)(5); see also FDA's guidance "General/Specific Intended Use," available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/generalspecific-intended-use-guidance-industry, which identifies the general principles that will be considered by FDA in determining when a specific indication for use is reasonably included within a general indication for use of a medical device for purposes of determining SE.

different disease stage) than the predicate device, clinical data may be needed to demonstrate SE if there is increased risk for the use of the new device in the higher risk population due to differences in the benefit-risk profile of the new device for the proposed indications for use when compared to the predicate device.

Example 1-B: A certain device is indicated for use in a specific anatomic location that is in proximity to critical organs. The manufacturer intends to pursue an indication for use in a different anatomic location that does not represent a new intended use and does not pose additional or different risks. In this scenario, non-clinical data may suffice to demonstrate SE because the indication for use for the predicate device (i.e., the currently-marketed device) represents a higher risk or similar risk scenario than that of the new device. As a result, no additional clinical data are likely to be necessary to demonstrate SE because the benefit-risk profile of the new device with the expanded indications for use is comparable to that of the predicate device.

Example 1-C: A device is indicated for use in a specific anatomic location, and a manufacturer wants to expand the indications for use to a different anatomic location for the same intended use. There are no other changes to the device. Based on what is known for this device type in the literature and through clinical experience, using the device in this new anatomic location presents an increased risk (for example, due to increased proximity to critical organs or structures, or the indication includes a procedure that is technically more risky or complex). Clinical data may be necessary to demonstrate SE between the new device with the expanded indications for use and the predicate device (i.e., the currently-marketed device) due to the increased risk that may adversely affect the benefit-risk profile of the new device when compared to the predicate device.

Example 1-D: A predicate laser device is indicated for treatment of a certain skin condition. A new laser device is indicated for treatment of a different skin condition that is not a new intended use. This new laser device utilizes a lower energy wavelength than the predicate device for treatment. Although the lower energy wavelength is not expected to present increased risk compared to the predicate device, clinical data may be needed to demonstrate that the new device has an equivalent benefit-risk profile to the predicate device, given that the new device may result in a different degree of benefit for treatment compared to the predicate device due to both the lower energy wavelength and the difference in skin conditions.

B. Scenario #2 – Differences in the technological characteristics

As discussed in the 510(k) Program Guidance, clinical data may be necessary to include in a 510(k) submission when there are differences between the technological characteristics of the new device and the predicate device that do not raise different questions of safety and effectiveness in order to establish that a new device performs equivalent to the predicate device despite the differences in those characteristics.[29]

[29] Section 513(i)(1)(A)(ii) of the FD&C Act.

The following factors should be considered in determining whether clinical data may be necessary to include in a 510(k) submission to demonstrate SE when there are differences between the technological characteristics[30,31] of the new device and the predicate device, as illustrated in examples 2-A, 2-B, and 2-C:

- Significant change in materials
- Significant change in device design
- Significant change in energy source
- Significant change in other device features

Example 2-A: An implanted device is used to provide anatomic support resulting in improved function. Most such devices are made of non-resorbable materials. Available performance data on such devices may not be applicable to a device comprised of resorbable material, which resorbs in vivo over time. For this difference in technology, assuming it does not raise different questions of safety and effectiveness, clinical data may be needed to support the SE determination.

Example 2-B: An IVD uses a monoclonal antibody as a critical reagent. If the manufacturer decides to change to a different clone from the previous antibody, clinical data may be needed to support the SE determination, as the differences in technological characteristics between the new IVD and the predicate IVD raise a question of whether the clinical performance of the new IVD can be expected to be equivalent to the clinical performance of the predicate IVD.

Example 2-C: A manufacturer chooses to add additional sizes of an implanted device to its existing line of cleared, implanted devices. No other changes are made to the design, materials, or other device features. The new sizes are within the minimum and maximum of the cleared, implanted devices of the device type. The new devices can likely be assessed using adequate non-clinical testing methods to determine SE to the predicate device. It is unlikely that clinical data would be necessary to evaluate this change in technological characteristic.

However, if the size of the new implanted device would become the new maximum or minimum size of all cleared, implanted devices of the device type, expanding the range of device sizes, provided that the intended use of the new device is the same as the predicate device, clinical data may be needed to support an SE determination.

[30] "Differences in technological characteristics" is defined in section 513(i)(1)(B) of the FD&C Act.

[31] The 510(k) Program Guidance describes overarching aspects for consideration regarding device design, materials, energy source, and other key technological features. For further information, please see Section IV.E of the 510(k) Program Guidance, available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/510k-program-evaluating-substantial-equivalence-premarket-notifications-510k.

C. Scenario #3 – SE cannot be determined by non-clinical testing

Clinical data may be necessary to include in a 510(k) submission when non-clinical testing, such as analytical, bench, and/or animal testing, is not adequate to establish that the new device is SE to the predicate device.[32]

The following factors represent considerations for determining when clinical data may be necessary to demonstrate SE as non-clinical testing may not be appropriate for a particular device, because:

- There is no model (e.g., analytical, bench, animal) available
- The available model(s) may not be adequate because the model has certain limitations that do not allow for an adequate assessment
- The model may not be predictive of clinical outcomes
- There are anatomical and/or pathophysiological species-specific questions that rely on clinical evidence

Example 3-A: For a new device with an intended use for treatment of schizophrenia, clinical data may be needed to demonstrate that the device is SE to the predicate device given the limited availability of non-clinical models and inadequate predictions of clinical outcomes for schizophrenia.

Example 3-B: A basic medical image management and processing system that adds a new organ-specific processing, filtering, or enhancement feature may need to submit clinical data to demonstrate that the new device is SE to the predicate device. This may occur in scenarios where there is no phantom that accurately models the organ in that imaging modality, so we recommend using clinical images as part of the device evaluation.

Example 3-C: For a device intended for use to support hemostasis, clinical data may be necessary to demonstrate that the new device is SE to the predicate device given the inadequacy of current bench and animal models to be predictive and representative of human performance due to the differences in coagulation pathways between animals and humans.

Example 3-D: For a device intended for use in screening donors of blood and blood products for transfusion-transmitted infections, clinical data may be necessary to demonstrate that the new device is SE to the predicate device given the inability of analytical testing to evaluate the clinical performance of the assay and the risks to the blood supply associated with incorrect results.

Example 3-E: For IVDs, including for an IVD intended for point-of-care use where the predicate device is not intended for point-of-care use, clinical data may be necessary to demonstrate that the new device performs equivalent and is SE to the predicate device. This is due to multiple

[32] Section 513(i)(1)(A) of the FD&C Act.

factors, including the variety of clinical environments and the diverse populations with which the device is intended to be used, which can affect the performance of the device and cannot be evaluated solely through analytical data.

Example 3-F: For a device intended for an aesthetic purpose (e.g., to treat acne scars, or to reduce wrinkles), it may be difficult to demonstrate the effectiveness of the new device solely with non-clinical (e.g., animal) data to determine SE to a predicate device. This is because there are no appropriate animal models for device types intended for aesthetic purposes, and validated aesthetic measures of effectiveness and the translatability of such measures in humans have not been established. For this reason, in many scenarios, clinical data may be necessary to demonstrate that a new device intended for an aesthetic purpose is SE to the predicate device.

D. Scenario #4 – Newly identified or increased risk for the predicate device

Although significant attention is applied to the design, testing, manufacturing, and evaluation of medical devices prior to their introduction into the marketplace, not all information regarding benefits and risks is available nor can be generally known at that time. New information about a device's safety, including unexpected adverse events, may become available once the device is more widely distributed and used in clinical practice.

In such cases, there may not be identified differences between the technological characteristics of new device and the predicate device that raise different questions of safety or effectiveness. However, there may be an awareness of new scientific information regarding a newly identified or increased risk of the predicate device, and clinical data may be needed to determine SE in light of the new scientific information.

As described in the 510(k) Program Guidance (Section IV.F), new scientific information may affect FDA's expectations concerning the type and level of performance data to be included in a 510(k) submission. FDA may learn of these new or increased risks for a device (compared to what was known prior to introduction into the marketplace) from voluntarily-reported adverse events or literature, or from other sources of real-world data (e.g., 522 postmarket surveillance studies[33,34] or recalls[35]), and incorporate that information into its review of premarket submissions and SE determinations. Information regarding new or increased risks for a device is often publicly communicated (e.g., via safety communication, guidance, advisory committee meeting) by FDA. When requesting clinical data during premarket review due to a new or

[33] For further information on postmarket surveillance studies, see FDA's guidance, "Postmarket Surveillance Under Section 522 of the Federal Food, Drug, and Cosmetic Act," available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/postmarket-surveillance-under-section-522-federal-food-drug-and-cosmetic-act.

[34] See FDA's webpage on the 522 Postmarket Surveillance Studies Program, available at https://www.fda.gov/medical-devices/postmarket-requirements-devices/522-postmarket-surveillance-studies.

[35] See FDA's webpage on Recalls, Market Withdrawals, & Safety Alerts available at https://www.fda.gov/safety/recalls-market-withdrawals-safety-alerts, as well as the Medical Device Recalls database, available at https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfRES/res.cfm.

increased risk, FDA intends to provide an explanation of the reason(s) for the request and why such information is necessary to determine whether the new device is SE, consistent with the FDA guidance on "Developing and Responding to Deficiencies in Accordance with the Least Burdensome Provisions."[36]

Whenever possible, FDA recommends that manufacturers should not use certain devices as predicate devices if they exhibit new or increased risks, especially if an alternative predicate device exists without the new or increased risk.[37] However, in certain circumstances, there may not be an alternative predicate device available without the new or increased risk. Devices that exhibit new or increased risks may lead FDA to consider the need for additional data, such as clinical data, in the premarket submissions for such technology, as illustrated in examples 4-A, 4-B, and 4-C.

Example 4-A: Through review of recalls, voluntarily-reported adverse events, and published scientific literature, FDA became aware of certain malfunctions for a particular device. However, based on FDA's assessment of the totality of clinical (e.g., published medical literature) and non-clinical data (e.g., non-clinical bench performance testing), FDA determined that detailed non-clinical testing, accompanied by appropriate instructions for use, could adequately demonstrate whether the risk for the new device was adequately mitigated by its design and technological features. FDA determined that additional clinical data was not necessary to demonstrate SE for new 510(k) submissions that may use this device as the predicate, provided that the appropriate non-clinical testing and certain labeling considerations are addressed in the 510(k) submission.

Example 4-B: A device was initially cleared by FDA without the inclusion of clinical data in the 510(k). Following introduction of the device into the marketplace, recalls and other postmarket surveillance data reviewed by FDA suggested safety concerns related to component failure in the device. After a thorough review of the available data, FDA issued a class-wide postmarket surveillance study order under section 522 of the FD&C Act for currently marketed devices for this device type and began requesting that clinical data be included in 510(k) submissions for new devices seeking marketing clearance for this device type to ensure an adequate safety profile prior to marketing.

Example 4-C: There was a device issue reported that could lead to significant patient injury in surgical procedures. For this cleared device, the primary evidence demonstrating SE in 510(k) submissions had been non-clinical design verification and validation testing of the technological characteristics of the device. The manufacturer voluntarily recalled the device, submitted a new 510(k) to address the issue, and included non-clinical and clinical performance data because the changes could significantly affect the safety or effectiveness of the device.[38] FDA issued device-

[36] Available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/developing-and-responding-deficiencies-accordance-least-burdensome-provisions.

[37] Please see FDA's draft guidance, "Best Practices for Selecting a Predicate Device to Support a Premarket Notification [510(k)] Submission," available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/best-practices-selecting-predicate-device-support-premarket-notification-510k-submission. When final, that guidance will represent FDA's current thinking on that topic.

[38] See 21 CFR 807.81.

specific guidance to outline recommendations for non-clinical and clinical performance testing for this device type.