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Benefit-Risk Factors to Consider When Determining Substantial Equivalence in Premarket Notifications (510(k)) with Different Technological Characteristics

Guidance for Industry and Food and Drug Administration Staff

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Preface

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Benefit-Risk Factors to Consider When Determining Substantial Equivalence in Premarket Notifications (510(k)) With Different Technological Characteristics

Guidance for Industry and Food and Drug Administration Staff

This guidance represents 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

A submitter of a premarket notification submission (510(k)) must demonstrate to the Food and Drug Administration (FDA) that the "new device" is "substantially equivalent" (SE)[1] to a legally marketed predicate device.[2] This guidance is intended to help 510(k) submitters demonstrate substantial equivalence. This guidance does not add new regulatory requirements for submitters, it does not change the 510(k) premarket review standard nor does it create extra or new burdens on what has traditionally been submitted in 510(k)s. FDA developed this guidance to improve the predictability, consistency, and transparency of the 510(k) premarket review process. Furthermore, this document is intended to serve as an aid for evaluating the benefit-risk profile of a new device in comparison to the predicate device.

The benefit-risk profile of a new device does not need to be identical to the predicate device for it to be SE to the predicate device. This document is intended to provide guidance when the benefit-risk profile of a new device is different from that of the predicate device. More specifically, FDA believes this document can be helpful in situations when there is 1) an increase in risk and increase or equivalent benefit or 2) a decrease in benefit and a decrease or equivalent risk when comparing a new device to a predicate device. In these situations, a benefit-risk assessment should be conducted comparing the benefits and risks of a new device to a predicate device. Such assessments may aid in

[1] In this guidance, "SE" also refers to "substantial equivalence."
[2] See section 513(i) of the Federal Food, Drug, and Cosmetic Act ("FD&C Act") (21 U.S.C. § 360c(i)).

the SE evaluation by assessing whether the new device is "as safe and effective" as the predicate device.

This guidance and associated recommendations for evaluating benefit-risk factors in the context of SE are consistent with the FDA guidance "The 510(k) Program: Evaluating Substantial Equivalence in Premarket Notifications [510(k)]"[3] (hereinafter, 510(k) Program Guidance), and least burdensome provisions in the FD&C Act and relevant FDA guidance.

FDA recognizes and anticipates that the Agency and industry may need up to 60 days to perform activities to operationalize the policies within the guidance. If a benefit-risk assessment as outlined in this guidance is not included in a 510(k) submission received by FDA before or up to 60 days after the publication of this guidance, FDA staff does not generally intend to request such information during the review of a 510(k) submission. FDA does, however, intend to review any such information, if submitted.

FDA's guidance documents, including this one, do not establish legally enforceable responsibilities. Instead, guidance documents 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 documents means that something is suggested or recommended but not required.

II. Background

A. The Statutory Standard for Substantial Equivalence

Submitters seeking device clearance must demonstrate to FDA in their 510(k) submission that the "new device" is SE to a "predicate device." For this guidance, a "new device" means a device within the meaning of section 201(h) of the FD&C Act (21 U.S.C. § 321(h)) that is not legally marketed. It can be either a completely new device or a modification of a legally marketed device that requires a new 510(k) under 21 CFR 807.81. A "predicate device" is a device that (1) was legally marketed prior to May 28, 1976 (preamendments device)[4], and for which a premarket approval (PMA) application is not required; ***or*** (2) has been classified or reclassified into class I or II;[5] ***or*** (3) has been found SE through the 510(k) premarket review process. For more information on the process required to demonstrate SE, refer to the 510(k) Program Guidance.

The standard for a determination of SE in a 510(k) premarket review is set out in section 513(i)(1)(A) of the FD&C Act (21 U.S.C. § 360c(i)(1)(A)), which states:

> "For purposes of determinations of substantial equivalence under subsection (f) and section 520(l), the term 'substantially equivalent' or 'substantial equivalence' means, with respect to a device being compared to a predicate device, that the device has the

[3] https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM284443.
[4] See Preamendments Status at https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/MedicalDeviceQualityandCompliance/ucm379552.htm.
[5] Section 513 of the FD&C Act (21 U.S.C. § 360c) establishes three device classes (class I, class II, and class III) and sets forth device reclassification procedures.

> same intended use as the predicate device and that the Secretary by order has found that the device—
>
> (i) has the same technological characteristics as the predicate device, or
>
> (ii)(I) has different technological characteristics and the information submitted that the device is substantially equivalent to the predicate device contains information, including appropriate clinical or scientific data if deemed necessary by the Secretary or a person accredited under section 523, that demonstrates that the device is as safe and effective as a legally marketed device, and (II) does not raise different questions of safety and effectiveness than the predicate device."

Therefore, in order to find a new device SE to a predicate device, FDA must first find that the devices have the "same intended use." FDA must then determine that the devices have "the same technological characteristics," or that any difference in technological characteristics does not raise different questions of safety and effectiveness and that the device is "as safe and effective" as the predicate device. "Different technological characteristics" is defined in section 513(i)(1)(B) of the FD&C Act (21 U.S.C. § 360c(i)(1)(B)), which states:

> "…the term '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."

If FDA determines that there are differences in the technological characteristics, between the new device and the predicate device, and that the different technological characteristics raise different questions of safety and effectiveness, FDA will determine that the new device is NSE to the predicate device. For more information on the critical decision-making points in the 510(k) premarket review process, refer to the 510(k) decision-making flowchart in Appendix A of the 510(k) Program Guidance (see adapted flowchart in **Figure 1**).

If FDA determines that the different technological characteristics do not raise different questions of safety and effectiveness, FDA will subsequently evaluate differences in the technological characteristics between the new device and the predicate device to determine impact on safety and effectiveness (i.e., whether the new device is "as safe and effective" as the predicate device). If a submitter made modifications to its own FDA-cleared device and submitted a new 510(k), FDA will evaluate the modifications and the information submitted to determine whether the modified device is still "as safe and effective" as the predicate device. In this situation, FDA's review focuses on the assessment of the modifications to device safety and effectiveness.

Under section 513(a)(2) of the FD&C Act (21 U.S.C. § 360c(a)(2)), FDA determines the "safety and effectiveness of a device" by "weighing any probable benefit to health from the use of the device against any probable risk of injury or illness from such use," among other relevant factors.[6]

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[6] The criteria for establishing safety and effectiveness of a device are set forth in 21 CFR 860.7. Subsection (b) notes, "[i]n determining the safety and effectiveness of a device…the Commissioner and the classification panels will consider

This guidance is consistent with the 510(k) Program Guidance and provides additional clarification on factors that FDA takes into consideration when evaluating the benefit-risk profile of a new device in comparison to a predicate device. As previously mentioned, this document provides guidance on when the submitter and FDA identifies a decrease in benefit and/or increase in risk between the new device and the predicate device.

B. Performance Data

When FDA is reviewing a 510(k) for a new device that has different technological characteristics than the predicate device, performance data may be warranted to assess whether the new device is "as safe and effective" as the predicate device. The type and quantity of performance data that may be needed to support a determination of SE depends upon the new device.[7] Valid scientific evidence may be generated from both non-clinical and clinical performance data. These types of performance data are evaluated by FDA during the premarket review process and can provide information relating to the benefit and risk factors discussed in this guidance.

Non-clinical testing can encompass an array of methods including, but not limited to, performance testing for product safety, reliability, characterization, human factors, usability, mechanical testing under simulated conditions, animal studies,[8] cell-based studies, and computer simulations. These tests characterize properties of the devices including, but not limited to, precision, reproducibility, linearity, wear, tensile strength, compression, flow rate, burst pressure, biocompatibility, toxicity, electromagnetic compatibility (EMC), sterility, stability/shelf-life data, software validation, and testing of synthetic samples.

Clinical data is not typically included in 510(k)s to demonstrate SE. However, when appropriate, valid scientific evidence can include randomized clinical trials in the appropriate target population, well-controlled investigations, partially controlled studies, studies and objective trials without matched controls, well-documented case histories conducted by qualified experts, certain reports of significant human experience, and testing on clinically derived human specimens (DNA, tissue, organ and cadaver studies).[9] Valid scientific evidence generated from clinical and/or non-clinical testing can be considered during FDA's review of the benefit-risk assessment.

When evaluating and comparing the benefits and risks of a new device to a predicate device, FDA evaluates the "probable" or "probability" of such risks and benefits. The use of the terms "probable" and "probability" in this guidance have the same connotation as in 21 CFR 860.7(b)(3), i.e., they refer to the probable benefit to patient health from the use of the device weighed against any probable injury or illness from such use. Hypothesis testing, formal concepts of probability and predictive probability, likelihood, etc. are typically important elements in the assessment of

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the following, among other relevant factors… (3) The probable benefit to health from the use of the device weighed against any probable injury or illness from such use." (21 CFR 860.7(b)). For additional information on FDA's safety and effectiveness review, see 21 CFR 860.7(d) and (e).

[7] See 21 CFR 860.7(c)(2).

[8] FDA supports the principles of the "3Rs," to reduce, refine, and replace animal use in testing when feasible. We encourage sponsors to consult with us if it they wish to use a non-animal testing method they believe is suitable, adequate, validated, and feasible. We will consider if such an alternative method could be assessed for equivalency to an animal test method.

[9] See 21 CFR 860.7(c)(2).

"probable" benefit and risk. In general, a "probable risk" and a "probable benefit"' do not include purely theoretical risks and benefits, but rather those that are supported by valid scientific evidence. FDA does not intend for the use of the term "probable benefit" in this guidance to refer to the regulatory term as used for the approval requirements for Humanitarian Device Exemptions (HDE) under section 520(m) of the FD&C Act (21 U.S.C. § 360j(m)), and FDA's implementing HDE regulations.

III. Scope

The 510(k) premarket review standard (i.e., SE of a new device when compared to a predicate device) does not require a new device to be identical to a predicate device. Under section 513(i) of the FD&C Act (21 U.S.C. § 360c(i)), FDA may determine that a new device is SE to a predicate device if, among other things, it has the same intended use. Differences in the indications for use, such as the population for which a device is intended or the disease a device is intended to treat, may not necessarily result in a new intended use.[10] In other words, FDA may find a new device with indications for use or technological characteristics that are different from those of the predicate device SE to a predicate device. Likewise, the benefit-risk profile of a new device does not need to be identical to be found SE to the predicate device.

This guidance document focuses on the steps of the 510(k) premarket review process after FDA finds that the intended use of the new device and predicate device are the same and have different technological characteristics that do not raise different questions of safety and effectiveness. Specifically, the guidance focuses on the step where FDA evaluates whether the new device is "as safe and effective" as the predicate device. As shown in the decision-making flowchart in **Figure 1**, this guidance focuses on the review steps after FDA has answered Yes to Decisions #1 and #2, and No to Decisions #3 and #4. (Note that the flowchart was adapted from Appendix A of the 510(k) Program Guidance.)

At this point in the review process, FDA determines whether the new device is "as safe and effective" as the predicate device by looking at the submitted performance data among other things. During the review, if FDA identifies an increase in risk and increase or equivalent benefit, or a decrease in benefit and a decrease or equivalent risk, when comparing a new device to a predicate device, a benefit-risk assessment may be beneficial to aid in the evaluation of SE or NSE. **Figure 1** highlights steps in the decision-making process where consideration of a benefit-risk assessment may be informative when reviewing a 510(k).

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[10] "[T]he term intended use means the general purpose of the device or its function, and encompasses the indications for use. The indications for use generally describe the disease or condition that will diagnose, treat, prevent, cure or mitigate, including a description of the patient population for which the device is intended. The indications include all the labeled patient uses of the device. As it relates to medical devices, the indications for use statement is a factor in determining a device's intended use; however, a change indications for use that requires submission of a new 510(k) does not necessarily mean that the device has a new intended use (such that the device would not be substantially equivalent under section 513(i) of the FD&C Act)." See the FDA guidance, "Deciding When to Submit a 510(k) for a Change to an Existing Device" (https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM514737) (internal citations omitted).

Benefit-risk factors are often considered when making a determination of SE or NSE for a new device that has the same intended use as the predicate device and different technological characteristics that do not raise different questions of safety and effectiveness. Some benefit and risk factors that FDA may consider are described below. Not all of the factors listed in this guidance will be applicable to each 510(k). **Section V** of this guidance provides examples of how these factors could be considered during a 510(k) premarket review.

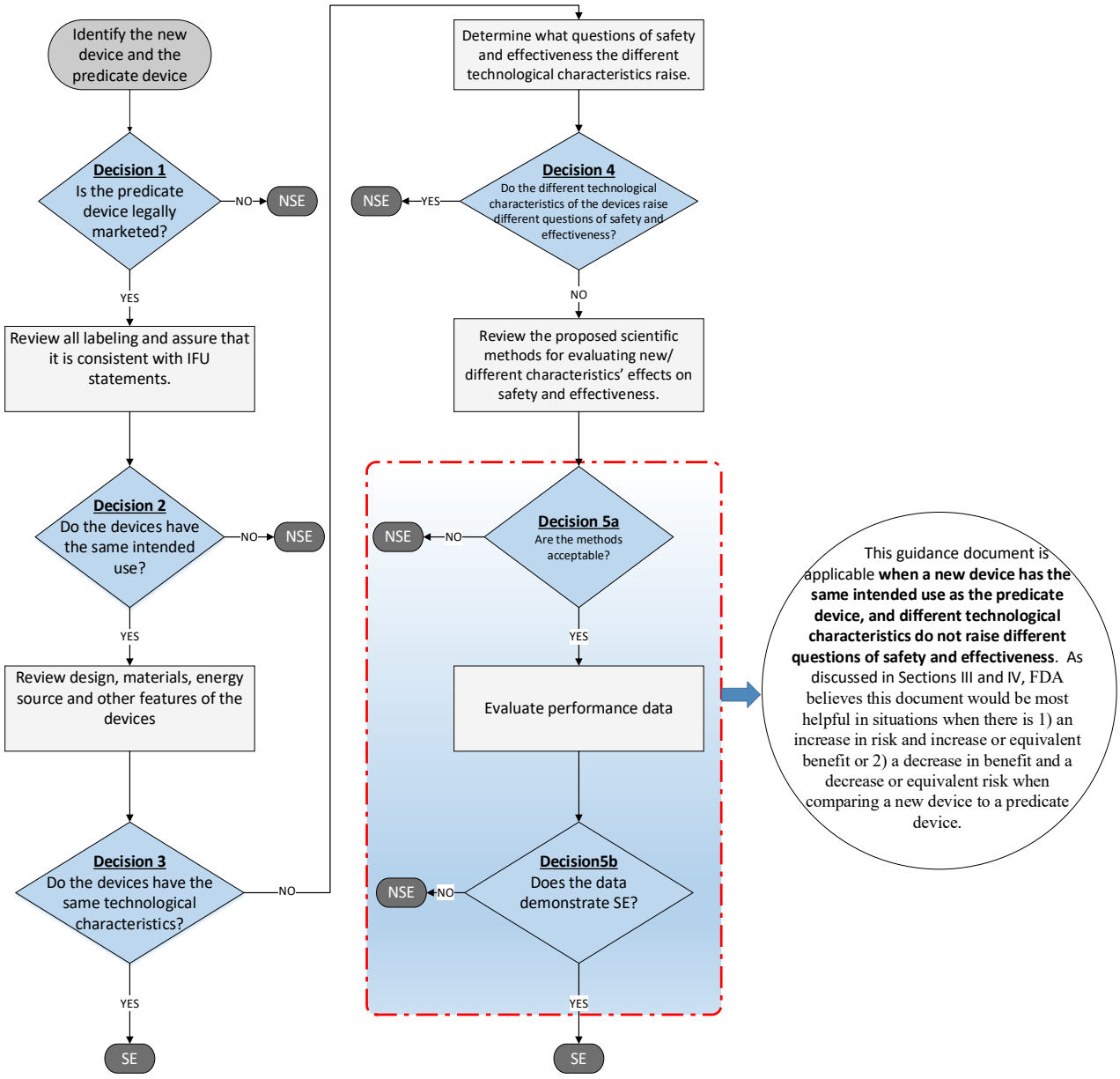

Figure 1: Decision-making flowchart (adapted from 510(k) Program Guidance) showing steps in the process when inclusion of a benefit-risk assessment could be helpful.

IV. Benefit and Risk Factors

The benefit-risk framework for 510(k) premarket reviews is fundamentally different from the benefit-risk framework that applies to devices in PMA or De Novo review. More specifically, in 510(k) premarket review, 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. Thus, during the 510(k) premarket review for a new device, it is important to understand the benefit-risk profile of the predicate device and previously cleared devices within the same type.[11] FDA may also consider whether prior evaluation of the benefit-risk profile for the same or similar device type is appropriate and still applicable based on postmarket and current real-world data.

As previously mentioned, the benefit-risk profile of a new device does not need to be identical to be as safe and effective as the predicate device. This section focuses on some of the factors that are taken into consideration when comparing the benefit-risk profile of a new device and predicate device to determine whether the new device is "as safe and effective" as the predicate device. An evaluation of these factors is important when there is an increase in risk and increase or equivalent benefit; or a decrease in benefit and a decrease or equivalent risk, when comparing a new device to a predicate device. In these situations, the factors in this guidance should be applied to help FDA determine if SE has been demonstrated. A benefit-risk assessment is not recommended for the majority of 510(k)s to support a determination of SE, including situations where there is an increase or equivalent benefit and a decrease or equivalent risk, when comparing a new device to the predicate device.

FDA may also consider the value that health-care professionals and patients place on the benefits. FDA understands that health-care professionals, who utilize devices in the treatment or diagnosis of patients with a disease or condition, may have developed their own insights into the benefits of the treatments that may vary from that of regulators. For more information on patient preference information (PPI) and patient-reported outcomes (PROs), refer to the FDA guidance "Patient Preference Information – Voluntary Submission, Review in Premarket Approval Applications, Humanitarian Device Exemption Applications, and De Novo Requests, and Inclusion in Decision Summaries and Device Labeling"[12] (hereinafter, "PPI Guidance").

When comparing the benefits and risks of a new device to a predicate device, there might be variability in the type or extent of benefits and/or risks. For that reason, FDA evaluates the differences between the benefits and risks of a new device to a predicate device, along with additional factors identified in **Section IV.C**. FDA evaluates the aggregate benefits, which includes, but is not limited to, consideration of the type, magnitude, probability, and duration of benefits. Likewise, FDA also evaluates the aggregate risks and considerations include, but are not limited to the severity, types, number, rates, and probability of risks.

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[11] See the FDA guidance, "Medical Device Classification Product Codes" (https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm285317.htm).
[12] https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM446680.

The benefit-risk assessment should identify and compare the differences in technological characteristics and how that could impact the new device's benefit-risk profile when compared to the predicate device.

Despite differences in the benefit-risk profile, in some circumstances the new device may be determined to be SE to the predicate device. As a part of our determination, FDA could also consider whether mitigation strategies, such as labeling revisions, could be implemented to address differences in the benefit-risk profile between a new device and a predicate device. Generally, if there is an increase in risk or decrease in benefit, FDA will likely find the new device NSE to the predicate device. See **Section V** of this guidance for examples of how FDA evaluates and considers benefits and risks during the review of a 510(k).

Both non-clinical and clinical data can play a role in FDA's benefit-risk determinations, and the factors discussed in this guidance may be informed by either type of data. In addition, both clinical and non-clinical testing can be used to assess the benefits and risks of a new device and can be used to assess the impact of risk mitigation measures. For information on the types of performance data that FDA can consider during the 510(k) premarket review, refer to Section F of the 510(k) Program Guidance.

A summary of the benefit-risk assessment can be included as part of the 510(k) summary consistent with 21 C.F.R. 807.92(b)(3). For more information on factors that are considered when assessing benefit, refer to **Section IV.A** below. For more information on factors that are considered when assessing risk, refer to **Section IV.B** below.

Below is an explanation of certain scenarios where a benefit-risk assessment could be useful. **Table 1** provides a guide for certain benefit and risk outcomes when the inclusion of a benefit-risk assessment in a 510(k) may be recommended. However, neither the table nor the benefit-risk outcomes explained below are intended to be decisional and instead represent the Agency's recommendation for when a benefit-risk assessment may or may not be helpful to include in a 510(k). This table should be used in conjunction with the guiding principles provided elsewhere in this guidance and not in isolation.

Decreased Benefit and Decreased/Equivalent Risk

If the aggregate benefit of a new device is decreased in comparison to the predicate and the risk level is decreased in comparison to that of the predicate device, FDA may determine the new device to be SE if the differences do not affect whether the new device is "as safe and effective" as the predicate device. However, if there is a decrease in benefit without a decrease in risk, FDA would likely find a device NSE to the predicate especially if the benefit-risk assessment confirms that the new device is not "as safe and effective" as the predicate device.

Equivalent/Increased Benefit and Increased Risk

FDA evaluates the nature of increased risk and degree of risk (e.g., severity, type, rate) in comparison to the predicate device to determine if the difference impacts whether the new device is "as safe and effective" as the predicate device. FDA may also consider whether additional

measures may help to mitigate the increase in risk. If there is an increase in aggregate risk and there is an increase in benefit associated with the new device as compared to the predicate device, FDA may determine the new device to be SE if the device is "as safe and effective" as the predicate. FDA will generally not find a new device SE to the predicate device when an increase in risk cannot be mitigated and is not accompanied by increased or equivalent benefit.

Table 1. Situations when a benefit-risk assessment could be recommended or not recommended as part of the evaluation of SE. [Note: This table should be used with the guiding principles provided in the rest of the guidance.]

	INCREASE IN RISK	**DECREASE/EQUIVALENT RISK**
INCREASE/ EQUIVALENT BENEFIT	**Conducting a benefit-risk assessment is recommended.*** The factors in this guidance should be used to assess the benefits and risks as part of the evaluation of substantial equivalence.	**Conducting a benefit-risk assessment as described in this guidance is likely not recommended to determine whether the new device is "as safe and effective" as the predicate device.** FDA will generally determine the new device SE to the predicate device when there is increase/equivalent benefit and decreased/equivalent risk.
DECREASE IN BENEFIT	**Conducting a benefit-risk assessment as described in this guidance is likely not recommended to determine whether the new device is "as safe and effective" as the predicate device.** FDA will generally determine the new device NSE to the predicate device when there is a decrease in benefit and an increase in risk.	**Conducting a benefit-risk assessment is recommended.*** The factors in this guidance should be used to assess the benefits and risks as part of the evaluation of substantial equivalence.

*FDA recommends conducting a benefit-risk assessment to determine if the new device is "as safe and effective" as the predicate device despite these differences. A summary of the benefit-risk assessment should be included in the 510(k) summary, when such information was important to FDA's determination that the new device is "as safe, as effective, and performs as well as or better than" the predicate device, consistent with 807.92(b)(3).

A. Assessment of the Benefits of Devices

Examples of possible device benefit(s) include, but are not limited to:

- Reduction in treatment time to achieve same effect;
- Improvement of mechanical properties to reduce probable likelihood of adverse events or to improve handling;
- Reduction of variability in device output;
- Improvements in clinical management, probability of survival, other aspects of patient health status (e.g., effect on patient management and quality of life, improvement of

patient function, prevention of loss of function, relief from symptoms), and patient satisfaction in the target population, which may be measured with the use of PROs; and

- For diagnostic devices specifically, benefit(s) in reference to the nature of the public health impact, could be based on a number of factors including:
    - Identification of a specific disease;
    - Provision of diagnosis at different stages of a disease;
    - Prediction of future disease onset;
    - Improvement of patient workflow;
    - Increase in efficiency or examination;
    - Provision of reproducible and quantifiable results contributing to the optimization of therapy and treatment; and
    - Improvement of patient outcome (e.g., well-being, health status, safety of patients) by facilitating fewer missed diagnoses (or the right diagnosis the first time, hence the correct treatment plan) and/or identification of patients likely to respond to a given therapy and therefore enable treatment of the disease or reduce/prevent its spread, which can often be measured through the use of PROs.

Endpoints denoting clinical benefit are usually measured directly, but in some cases may be demonstrated by use of surrogate endpoints that are reasonably likely to predict clinical benefit.

FDA assesses information provided in a 510(k) concerning the extent of probable benefit(s) by considering, among others, the following factors individually and in aggregate when making a comparison to the predicate device:

(1) Magnitude of the Benefit(s)

Benefits are often assessed along a scale or according to specific endpoints or criteria. The criteria should be established based on scientific and/or clinical rationale. Variation in the magnitude and type of benefit across a population is considered. The magnitude of benefit for diagnostic devices is defined in large part by the accuracy and reproducibility of test results and by the expected effect of clinically applying those results.

(2) Probability of the Patient Experiencing One or More Benefit(s)

Based on the data provided, it is sometimes possible to predict which patients may experience a benefit, whereas other times this cannot be accurately predicted. The data may show that a benefit may be experienced only by a small portion of patients in the target population or may occur frequently in patients throughout the target population. It is also possible that the data will show that different patient subgroups are likely to experience different benefits or different levels of the same benefit. If the subgroups can be identified, the device may be indicated for those subgroups. In some cases, however, the subgroups may not be identifiable. In addition, the magnitude and probability can be considered together when weighing benefits against risks. That is, a large benefit experienced by a small proportion of participants may raise different considerations than does a small benefit experienced by a large proportion of participants.

(3) Duration of Effect(s)

This factor refers to how long the benefit can be expected to last for the patient. Some treatments could be curative, whereas some may need to be repeated frequently over the patient's lifetime. To the extent that it is known, the duration of a treatment effect may directly influence how its benefit is defined. Treatments that must be repeated over time may introduce greater risk or the benefit experienced may diminish each time the treatment is repeated.

B. Assessment of the Risks of Devices

Risks of devices can take many forms, including impact on:

- Device performance (e.g., device failure and its impact on adverse events);
- Clinical management;
- Patient health status, often measured using PROs (e.g., negative effect on patient management and quality of life, decline of patient function, loss of function, worsening symptoms); and
- Patient tolerability.

FDA assesses the extent of the probable risk(s)/harm(s) by considering, among others, the following factors individually and in the aggregate as compared to the predicate device:

(1) Severity, Types, Number, and Rates of Harmful Events

For the purpose of this guidance, "rate of harmful events" refers to the number of harmful events per patient or the number of harmful events per unit of time associated with the use of the device. We identify each type of harm individually for the purpose of clarifying which of the more commonly recognized harms FDA might consider in benefit-risk assessments. In making benefit-risk assessments, FDA may consider each type of harm individually and in aggregate.

- **Device-related serious adverse events:** These are events that may have been or were attributed to the use of the device and caused or contributed to a death, injury, or illness that is life-threatening, resulted in permanent impairment or damage to the body, or required medical or surgical intervention to prevent permanent harm to the body.[13]
- **Device-related non-serious adverse events**: These are events that may have been or were attributed to the use of the device and do not meet the criteria for classification as a device-related serious adverse event.
- **Procedure-related complications:** These are events that caused harm to the patient, would not be included under serious or non-serious adverse events, and indirectly resulted from use of the device. Examples include anesthetic-related complications associated with the implantation of a device or risks associated with the collection of human biological materials. The latter consideration affects the risk profile of *in vitro*

[13] See generally 21 CFR 803.3(w) (defining "serious injury" for purposes of 21 CFR part 803).

diagnostic devices when the biological material is collected via an invasive procedure for the purpose of performing the diagnostic test.

(2) Probability of a Harmful Event

The probability of a harmful event is the proportion of the intended population that could be expected to experience a harmful event. FDA could factor whether an event occurs once or repeatedly into the measurement of probability.

(3) Probability of the Patient Experiencing One or More Harmful Event(s)

Based on the data provided, it is sometimes possible to predict which patients may experience a harmful event, whereas other times this cannot be accurately predicted. The data may show that a harmful event may be experienced only by a small portion of patients in the target population or may occur frequently in patients throughout the target population.

(4) Duration of Harmful Events (i.e., How Long the Adverse Consequences Last)

Some devices can cause temporary, minor harm; some devices can cause repeated, but reversible harm; and other devices can cause permanent, debilitating injury. FDA may also consider the severity of the harm along with its duration.

(5) Risk from False-Positive or False-Negative Results for Diagnostic Devices

If a diagnostic device gives a false-positive result, the patient might, for example, receive an unnecessary treatment and incur the potential risks that accompany that treatment or might be incorrectly diagnosed with a serious disease. Additionally, the patient might not receive effective treatment (thereby missing out on the benefits that treatment could confer) or might not be diagnosed with the correct disease or condition. These risks and other risks arising from false test results should be considered in terms of their likelihood and severity.

In addition to the type of risks discussed in (1) to (5) above, FDA also considers the number of different types of harmful events that can result from using the device and the severity of the aggregate effect. When multiple harmful events occur at once, they can have a greater aggregate effect. For example, there may be a harmful event that is considered minor when it occurs on its own, but when it occurs along with other harmful events, the aggregate effect on the patient may be substantial.

In circumstances where clinical data are not warranted to demonstrate SE, other types of valid scientific evidence may be used to assess probable risks of the technological changes that address the considerations above (e.g., rates of failures, severity of failures, duration of harmful event, etc.). These include, but are not limited to, the risk analysis for the product, reports of simulated

use tests, modeling, animal testing, and, where applicable, a review of conformance with FDA-recognized consensus standards.

C. Additional Factors in the Assessment of the Benefits and Risks of Devices

(1) Uncertainty

When determining if a new device is "as safe and effective" as a predicate device, we consider the extent of certainty of the benefits and risks of a device. In the context of this guidance, greater uncertainty may arise from a lower level of available evidence with regards to the benefit-risk profile for a new device. Factors such as less than optimal design or less than optimal conduct of bench testing, animal or clinical studies, or inadequate analysis of data can render the outcomes of the test or study less reliable or invalid, and may not provide the degree of information to fully understand the effects of the new technology. Additionally, for certain device types where clinical data are warranted to determine SE, it is important that the clinical study is adequately designed; failure to adequately design a clinical study can introduce uncertainty into the benefit-risk assessment for the device, which may not support an SE determination.

(2) Characterization of the Disease/Condition

During review of the 510(k), FDA may consider the following:

- the treated or diagnosed disease/condition and its clinical manifestation;
- how the disease affects the patients who have it; and
- how and whether a diagnosed disease/condition is treated and the condition's natural history and progression (i.e., does it get progressively better or worse over time for the patient and at what expected rate?).

(3) Innovative Technology

When a new device has technological improvements that are important for public health, FDA may accept greater uncertainty in an assessment of benefits and risks as compared with the predicate device than for other established technologies in order to facilitate patient access to these innovative technologies, if FDA's overall assessment is sufficiently balanced by other factors to support a determination that the new device is "as safe and effective" as the predicate device. Innovative changes are evaluated on a case-by-case basis in terms of the degree of benefit.

(4) Patient Tolerance for Risk and Perspective on Benefit

Risk tolerance varies among patients and affects individual patients' decisions as to whether higher risks in the new device's technology as compared to the predicate device are acceptable in exchange for a higher probable benefit. When evaluating benefits and risks, FDA recognizes that

PPI studies of risk may identify patients who are reasonably willing to accept a higher level of risk to achieve a higher probable benefit or an additional type of benefit (e.g., an improvement in quality of life stemming from greater comfort or ease of use). At the same time, other patients may be more risk-averse. Patient-centric assessments and PPI studies should take into account both the patient's willingness and unwillingness to use a device or tolerate risk when evaluating the relative safety and effectiveness of the new device in comparison to the predicate. FDA may also consider evidence relating to patients' perspectives on what constitutes a benefit, as some set of patients may value a benefit more than others.

Assessing patient tolerance for risk and perspective on benefit via PPI studies may be an informative and helpful factor in evaluating the overall benefit-risk profile of a device and whether a new device is as safe and as effective as a predicate device. FDA recommends that any submitter who is considering developing or presenting studies and/or data concerning patient risk tolerance or perspective on benefit in their 510(k) consult the PPI Guidance. Although the PPI Guidance is not specific to 510(k) submissions, the concepts and recommendations in this guidance may be helpful for manufacturers who intend to submit PPI studies in a 510(k) as part of a benefit-risk assessment.

We also recommend discussing your plans at an early stage with the appropriate FDA review Division using the Pre-Submission Program described in the FDA guidance "Requests for Feedback on Medical Device Submissions: The Pre-Submission Program and Meetings with Food and Drug Administration Staff."[14]

(5) Benefit for the Health-Care Professional, Patient, or Caregiver

FDA recognizes that certain devices, such as surgical tools that allow different techniques or devices that positively affect ongoing patient management, may benefit health-care professionals or caregivers by improving the way they care for the patients and consequently improving patient outcomes. Additional examples are surgical instruments with improved ergonomic design for ease of use or patient monitoring devices with wireless capabilities. For these devices, submitters may consider developing or presenting valid measurement methods and/or data concerning perspective on benefit for health-care professionals or caregivers. FDA recommends that any submitter who is considering developing or presenting valid measurement methods and/or data concerning perspective on benefit for health-care professionals or caregivers in their 510(k) have early interaction with the appropriate FDA review division.

(6) Risk Mitigation

The use of mitigations, when appropriate, can minimize the probability of a harmful event occurring and improve the benefit-risk profile. Even if a new device has an increased risk and if the risk is appropriately mitigated, FDA may determine that the new device has a comparable benefit-risk profile to the predicate device and therefore determine that the new device is "as safe

[14] https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM311176.

and effective" as the predicate device. The most common form of risk mitigation is to include appropriate information within labeling (e.g., warnings, precautions, contraindications). Some risks can be mitigated through other forms of risk communication, including training and professional and patient labeling. For *in vitro* diagnostic devices, risks may be mitigated by the use of complementary or supplementary diagnostic tests and/or controls or when used in conjunction with other available information, including clinical symptoms and family history.

(7) Postmarket Data

The use of devices in a postmarket setting can provide a greater understanding of their risks and benefits and the risks and benefits of similar devices. When reviewing a new device and assessing different technological characteristics in accordance with this guidance, FDA may consider postmarket data (e.g., literature, recalls, registry data, medical device reports) collected on marketed devices of the same type. This assessment may clarify the magnitude and effect of mitigations and may provide additional information when evaluating benefits and risks of the new device in accordance with an SE determination. In some cases, postmarket information can be used to confirm that certain risks have been mitigated or to identify which patients are most likely to suffer adverse events. In addition, FDA has the authority to require postmarket surveillance for certain class II devices[15] and may order postmarket surveillance for a new device that is expected to have significant use in pediatric populations as a condition to an SE determination.[16] Postmarket surveillance for a new device that is expected to have a significant pediatric use can serve to complement premarket data.

Furthermore, section 513(i)(1)(C) of the FD&C Act (21 U.S.C. § 360c(i)(1)(C)) requires FDA to consider the use of postmarket controls in the review of 510(k)s, stating "[t]o facilitate reviews of reports submitted to the Secretary under section 510(k), the Secretary shall consider the extent to which reliance on postmarket controls may expedite the classification of devices…" As discussed in the FDA guidance "The Least Burdensome Provisions of the FDA Modernization Act of 1997: Concept and Principles,"[17] reliance on postmarket controls (e.g., Quality System regulations, postmarket surveillance, and the Medical Device Reporting requirements) should be considered as a mechanism to reduce the extent of premarket data for 510(k)s, while still ensuring the safety and effectiveness of the device. In some cases, FDA may accept greater premarket uncertainty regarding a device's benefit-risk profile through greater reliance on postmarket controls, such as postmarket surveillance where applicable, in order to reduce the premarket burden for a 510(k), if FDA's overall assessment is sufficiently balanced by other factors to support SE and taking into account FDA's limitations with respect to requiring postmarket studies for 510(k)s.

[15] See section 522 of the FD&C Act (21 U.S.C. § 360l).
[16] See section 522(a)(1)(B) of the FD&C Act (21 U.S.C. § 360l(a)(1)(B)).
[17] https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM085999.

V. Examples of Benefit-Risk Evaluation

The examples below are hypothetical or simplified real-world situations and are offered only for illustrative purposes, i.e., no example is a complete assessment of the benefit-risk issues associated with any actual 510(k). The decisions described in these examples are not predictive of future FDA decisions; rather, they are hypothetical outcomes and are intended only to demonstrate how FDA could consider the factors described in this guidance when evaluating benefits and risks during a 510(k) premarket review. Similar scenarios or devices may result in different clearance outcomes depending on the individual performance characteristics of a particular device, the population for which it is indicated, and the context. These examples are not intended to provide device-specific data recommendations for the assessment of the factors.

Because this guidance document focuses on the part of the SE decision-making process occurring after FDA finds that the intended use of the new device and predicate device are the same, and that any differences in technological characteristics do not raise different questions of safety and effectiveness, these examples focus on the use of benefit-risk assessments after Decision #4 of the SE decision-making process, as described in **Figure 1**.

A. Example 1: Change in Device Design

Scenario: A manufacturer submitted a 510(k) for a powered rongeur for use during spinal surgery that utilizes new designs, i.e., a different shape and a different, deeper cutting action than the identified predicate device. The new design presents increased risk because the new cutting action exposes additional anatomy of the patient to an increased risk of injury. On the other hand, the new design expedites the cutting process and minimizes the time needed for surgical procedures, and its shape allows easier access to specific anatomic regions than the available predicate devices. After reviewing bench testing, FDA noted that the bench testing was not designed to address the increased risk. The manufacturer provided performance data to demonstrate that the risks noted by the review team had very low incidence. The animal study made a direct comparison to the predicate device. The new device demonstrated shorter surgery time, and the results of a survey of the participating surgeons emphasized the ease of accessing more difficult anatomic areas compared to the predicate device, therefore reducing the likelihood of injury to neighboring tissue when accessing the difficult-to-reach anatomical areas in the patient. The device is also available in a range of sizes which also raises concerns about elevated risk if larger sizes than necessary are used because this resulted in higher adverse event rates in the animal study.

Is a benefit-risk assessment recommended?

Yes. A benefit-risk assessment should be conducted to assess the increase in risk and increase in benefit.

Benefits: Compared to the predicate device, the new device offers surgeons an option to access specific anatomic areas around the spine more easily with a lower likelihood of injury to neighboring tissue. In some cases, surgeons may prefer to use this tool rather than the predicate

because the new device can offer a deeper cutting action which was demonstrated in the animal study to shorten the duration of surgery. In addition, shorter surgery time results in less time under anesthesia and less exposure to risk of infection.

Risks: The new deeper cutting action introduces higher risks of injury to the dura, arteries, veins, and nerve roots than the predicate device. The manufacturer provided data from an animal study to address the higher level of risks associated with the new deeper cutting action. The data provided demonstrate that the probability of harm is low; however, using the incorrect size of the device was found to increase risk of injury in the animal study.

Additional Factors:

Risk Mitigation: To address the concern of elevated risk due to using an incorrectly sized device, labeling is used to identify the proper size to be used based on anatomical measurements made before surgery.

Benefit for the Health-Care Professional or Caregiver: The new design allows for easier use by the surgeons as demonstrated in the survey data provided by the manufacturer, thereby reducing risk of injury to the patient.

SE Analysis: The technological differences present an increased risk of injury to the dura, arteries, veins, and nerve roots. The manufacturer provided animal study data to address these additional risks and to demonstrate that the probability of such harms is low. The manufacturer's labeling further mitigates risk observed in the animal testing by identifying methods to help the surgeon choose the proper device size. Furthermore, the animal study demonstrated that the new device shortened the surgery time compared to the predicate device, and surveys of participating surgeons emphasized the benefit of easier access to specific anatomic regions around the spine, thereby reducing risk of injury to the patient. Although the probable risk may be slightly higher than that of the predicate device due to the nature of cutting, the increase was demonstrated to be minimal. In addition, the non-clinical performance data did demonstrate benefit from the new shape and cutting action in terms of shortened surgical time and easier access. Because the increase in risk is accompanied by an increase in benefit and the new device would likely have a comparable benefit-risk profile to the predicate device for the indicated patient population, this device would likely be found SE.

B. Example 2: Change in Technology and Possible Change in Principle of Operation

Scenario: A self-contained device uses a low-level laser therapy for the treatment of toenail fungus (onychomycosis). The new device uses a different wavelength than the predicate device that was shown to produce different photo-biological effects, have a power level much lower than the predicate device, and have a constant energy delivery sequence in comparison to the pulsing sequence of the predicate device. For the treatment of onychomycosis, the purported mechanism of action is either a photo-biological process in which the laser wavelength interacts with chromophores within the fungal cells resulting in cell death or may involve a thermal effect on the fungal cells at temperatures below those required for tissue coagulation or tissue

vaporization. Due to the differences in technological characteristics and possible changes in principles of operation between the new device and predicate device, the manufacturer provided clinical data to compare their device to the predicate device. The device would have equivalent benefit as the predicate device if a majority of the subjects were responders, where a responder is a subject for whom the toenail is effectively treated according to predefined success criteria. The clinical data demonstrated that the responder rate was lower in the group treated with the new device. The new device is considered to pose a lower risk than the predicate device because the power level of the new device is significantly lower.

Is a benefit-risk assessment recommended?

Yes. A benefit-risk assessment should be conducted to assess the decrease in risk and decrease in benefit.

Benefits: The new device offers an alternative treatment modality than the predicate device. However, the study failed to meet the primary endpoint, as data did not support that the majority of the responders saw treatment success.

Risks: The new device offers lower risk to the subject with a reduction of power and offers minimal side effects when compared to the predicate device. Other risk mitigations include the wearing of laser safety protective glasses to prevent accidental eye damage from laser exposure.

Additional Factors:

Uncertainty: The results of the clinical study raised significant concerns regarding the reliability of the observed benefit of the new device. The proportion of responders was lower than desired. In addition, there were significant data inconsistencies regarding the manufacturer's photographs and data set in comparison to the predicate device.

SE Analysis: Due to the differences in technological characteristics between the new device and predicate device, the manufacturer provided clinical data to establish SE. The clinical data failed to demonstrate the new device provided benefit for the majority of treated patients. In addition, the provided data presented significant inconsistencies and was considered not reliable. Although the new device imparts less risk, the benefit of the device is considerably smaller than the predicate device. Additionally, there is considerable uncertainty with the small benefit observed. Therefore, this device would likely be found NSE based on a lack of adequate performance data.

C. Example 3: New Device with Higher Risk of Malfunction

Scenario: A manufacturer submitted a 510(k) for an external infusion pump that can be used in an ambulatory, portable setting. The device manufacturer claimed SE to a standalone external infusion pump which is used within the hospital setting for controlled intravenous (IV) delivery of fluid and medications to patients. The new device utilizes a new, compact, portable platform that may be used to deliver IV therapy to a patient who is in transit via ambulance or other transport, such as a helicopter. Unlike the predicate device, the new device operates fully on a battery and has a smaller, simpler user interface than the predicate device. Because the new

device is mobile, it can serve as a medical countermeasure to provide therapy to patients as part of a public health response to a chemical, biological, radiological, nuclear, or high-yield explosive (CBRNE) event.[18]

The user interface was evaluated and found to be adequate in achieving device performance without additional risk. However, there was concern that the new device has a higher risk of damage-related malfunction than the predicate device due to the ambulatory environment in which it is used which could result in harm to the patient due to under-infusion, over-infusion, or delay of therapy. To address the concern, the manufacturer performed bench studies to assess the durability of the device when exposed to simulated, worst-case conditions in ambulatory transport scenarios. This included, but was not limited to, humidity tests, temperature exposure tests, mechanical forces (impact, vibration, etc.), fluid ingress, pressure altitude, and occlusions. Bench testing results demonstrated an increased risk of calibration drift over repeated uses in ambulatory environments. To mitigate this risk, the manufacturer changed the labeling to instruct the user to perform frequent preventive maintenance.

Is a benefit-risk assessment recommended?

Yes. A benefit-risk assessment should be conducted to assess the increase in risk and increase in benefit.

Benefits: Compared to the predicate device, the compact, portable platform of the new device enables the health-care professional to extend intravenous (IV) therapy from the hospital care setting into the mobile setting. It is important to consider that in the cramped environment of a transport vehicle, such as an ambulance or helicopter, the compact profile of this new device's design enables the health-care professional to accommodate the critical care needs of the patient which may include ventilator support, cardiac monitoring, and suction. In an emergency setting, vehicles are often modified to accommodate the transport of multiple patients. In this scenario, where the space for patients and health-care professionals is already constrained, the compact profile of durable medical equipment becomes an essential characteristic. In addition, the device can operate in various temperature and humidity conditions, as demonstrated by the bench data, thereby increasing its utility as a medical countermeasure in response to CBRNE events.

Risks: The environments in which the new device is used introduce increased risks of damage to the device while it is an ambulatory setting, such as in an ambulance or helicopter. The manufacturer provided non-clinical testing demonstrating that calibration may drift over time due to the mechanical forces that the device is exposed to while in ambulatory transport. This calibration drift may cause the pump to deliver more or less fluid than the amount programmed

[18] For information on FDA's policies for authorizing the emergency use of medical products under section 564 of the FD&C Act (21 U.S.C. § 360bbb-3), see the FDA guidance, "Emergency Use Authorization of Medical Products and Related Authorities" (https://www.fda.gov/RegulatoryInformation/Guidances/ucm125127.htm). Section 564 of the FD&C Act permits the FDA Commissioner to authorize the use of an unapproved medical product or an unapproved use of an approved medical product during a declared emergency involving a heightened risk of attack on the public or U.S. military forces, or a significant potential to affect national security, provided that certain criteria are met.

into the device. Testing demonstrated that the calibration drifts occurs only after repeated exposures to the ambulatory environment.

Additional Factors:

Benefit for the Health-Care Professional or Caregiver: The predicate device does not allow the health-care professional to extend IV therapy into the mobile setting. This new device allows health-care professionals to use the pump in the mobile setting to accommodate the critical care needs of the patient, which may include ventilator support, cardiac monitoring, and suction in an emergency environment.

Risk Mitigation: The manufacturer demonstrated that increased preventive maintenance will reduce the risk to health associated with possible calibration drift. Therefore, the manufacturer changed the labeling to instruct the user to perform preventive maintenance after 100 hours of ambulatory use, which is more frequent than the predicate device's instructions regarding preventative maintenance.

SE Analysis: Unlike the predicate device the new device is fully battery-operated, compact, and contains a simplified user interface so that it can be used in a mobile ambulatory setting. The higher risk of damage-related malfunction in the ambulatory environment could result in under-infusion, over-infusion, or delay of therapy. The manufacturer provided non-clinical performance data that confirmed the durability of the device in simulated, worst-case ambulatory conditions. These data revealed that the device is prone to calibration drift over repeated use in ambulatory settings. To mitigate this risk, the manufacturer changed the labeling to instruct the user to perform more frequent preventative maintenance. The increased benefit of providing therapy to patients in transit or to a mass number of patients in a public health emergency outweighs the increased risk of calibration drift identified with the ambulatory platform for an infusion pump. Because the increase in risk, mitigated by statements in the labeling, is accompanied by an increase in benefit, the new device would likely have a comparable benefit-risk profile for the indicated patient population to the predicate device, and this device would likely be found SE.

D. Example 4: Material Differences Resulting in Different Device Performance

Scenario: The manufacturer of a male condom composed of synthetic material claimed SE to a natural rubber latex condom. The only technological difference between the two devices is the material, i.e., synthetic versus natural rubber latex. There was concern that the new material may not perform as well as the natural rubber latex material and could result in breakage or slippage during sexual intercourse. These risks can be evaluated in a clinical study comparing the performance of the synthetic condom to a cleared natural rubber latex condom (predicate device). The new device manufacturer sought to demonstrate non-inferiority to natural rubber latex condoms for a primary endpoint evaluating clinical failure (slippage and breakage) during sexual intercourse. The manufacturer performed the clinical study, which met the primary endpoint, but the slippage rate was slightly higher than natural rubber latex condoms.

Is a benefit-risk assessment recommended?

Yes. A benefit-risk assessment should be conducted to assess the increase in risk and increase in benefit.

Benefits: This device provides another option for contraception and prophylaxis, which is particularly beneficial for users and their partners that are allergic to natural rubber latex.

Risks: The new material may lead to increased slippage and breakage of the condom during sexual intercourse, which increases the risk of undesired pregnancy and/or transmission of sexually-transmitted infections (STIs). The clinical study showed an equivalent rate of clinical failure for the synthetic condoms compared to natural rubber latex condoms; however, the occurrence of slippage was slightly higher.

Additional Factors:

Risk Mitigation: To mitigate the risk associated with the slightly higher slippage rate revealed by the clinical study, a warning was placed on all labeling that states that the device should be used only if the user has an allergy to natural rubber latex.

SE Analysis: The new device provides another contraception and prophylaxis option, which is particularly beneficial for patients and their partners who are allergic to natural rubber latex. However, as compared to the predicate device, the new device may have the potential for increased slippage during sexual intercourse, resulting in an increased risk of undesired pregnancy and transmission of STIs. This risk between the new device and the predicate device is partially mitigated by warnings on the labeling. Because the increase in risk, which may be partially mitigated by warnings on the labeling, is accompanied by an increase in benefit, the new device would likely be found SE.

E. Example 5: Different Principle of Operation Used to Achieve Same Therapeutic Outcome

Scenario: A device that exerts pressure on the mouth is used to treat obstructive sleep apnea in adults. In comparison to the predicate device, which is the first-line treatment for this condition, the new device has a different principle of operation to achieve the same intended therapeutic outcome. There was concern that the new principle of operation could potentially partially close the oral cavity, restricting the user to breathing through the nose. The bench data reveal a higher level of pressure exerted by the new device as compared to the predicate device, but the manufacturer provided bench performance data to show that the level of pressure would not hold the mouth closed in the event of nasal obstruction. In addition, clinical data from a 28-day study evaluating the ability of the device to reduce the apnea-hypopnea index (AHI) from baseline as compared to the predicate device was provided. The study results showed that the new device had a reduction in AHI, but less than that of the predicate device. The study also revealed that patient compliance with the device was lower than the predicate due to the higher pressure exerted by the device and had a higher complication rate compared to the predicate.

Is a benefit-risk assessment recommended?

No. A benefit-risk assessment is not recommended because there is increased risk and a decreased benefit. FDA will generally determine the new device NSE to the predicate device under these circumstances.

F. Example 6: Comparative Testing Resulting in Substantially Different Results

Scenario: The manufacturer of a new test for measurement of prothrombin time (PT) international normalized ratio (INR) and coagulation factor levels produces a critical reagent through recombinant DNA technology, rather than as a multicomponent extract of animal tissue. For samples with prolonged PT, the PT results from the new test showed positive bias, compared to results from the predicate device. INR results from the two devices were in better agreement across the measurement range but included few samples with markedly elevated INR. Calibrated assays for fibrinogen and coagulation factors II, V, VII and X showed strong correlation between the new device and the predicate device, though times required for clot formation at low factor levels were longer with the new device than with the predicate device. Precision and inter-day/inter-lot studies showed that results from the new device were more reproducible than are results from the predicate device. Studies of known PT interferents, at physiologically relevant concentrations, showed no unexpected effect on results from the new assay. Review of recent postmarket medical device reports (MDRs) for PT devices showed that the only previously cleared PT product incorporating a (different) recombinant DNA reagent is subject to interference from an antibacterial drug that has not previously been associated with PT interference. The mechanism of the interference (involving the recombinant reagent and another chemically defined assay component) is well-defined. Bench studies showed no interference with the new product by the antibacterial drug associated with the MDRs or by currently marketed members of that antibacterial drug's class.

Is a benefit-risk assessment recommended?

No. A benefit-risk assessment is not recommended because there is equivalent risk and an increased benefit. FDA will generally determine the new device SE to the predicate device under these circumstances.