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

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Draft Guidance for Industry and Food and Drug Administration Staff

DRAFT GUIDANCE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

Draft Guidance for Industry and Food and Drug Administration Staff

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. Introduction

A submitter of a premarket notification submission (often referred to as a 510(k)) must demonstrate to the Food and Drug Administration (FDA) in its 510(k) submission that the new device is "substantially equivalent" (SE) to a legally marketed (predicate) device.[1] At certain points in the substantial equivalence analysis, the probable benefits and risks of a new device as compared to a predicate device may be relevant. The benefit-risk factors discussed in this guidance may assist FDA reviewers in making substantial equivalence determinations and may help accommodate evolving technology during the 510(k) premarket process. This guidance may also help submitters of 510(k) premarket notifications demonstrate substantial equivalence in their premarket submissions. FDA has developed this guidance in order to improve the predictability, consistency, and transparency of the 510(k) premarket review process. This guidance does not change the 510(k) premarket review standard or create extra burden on a submitter of a 510(k) to provide additional performance data from what has traditionally been submitted during the review process for 510(k) submissions.

[1] See section 513(i) of the Federal Food, Drug & Cosmetic Act (FD&C Act) (21 U.S.C. § 360c(i)).

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

A submitter of a 510(k) submission must demonstrate to FDA in its 510(k) that the new device[2] is SE to a "predicate device."[3] See section 513(i) of the FD&C Act (21 U.S.C. § 360c(i)). A predicate device is a device that (i) was legally marketed prior to May 28, 1976 (preamendments device), for which a premarket approval application (PMA) is not required; ***or*** (ii) has been classified or reclassified into Class I or II;[4] ***or*** (iii) has been found SE through the 510(k) process. See 21 CFR 807.92(a)(3).

The standard for a determination of substantial equivalence in a 510(k) review is set out in section 513(i) of the FD&C Act (21 U.S.C. § 360c(i)):

> Substantial Equivalence
>
> (i)(1)(A) 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 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.

[2] For the purpose of this guidance document, 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.

[3] For more information on the 510(k) program, see FDA's Draft Guidance, *The 510(k)Program: Evaluating Substantial Equivalence in Premarket Notifications [510(k)]* ("510(k) Program"), issued on December 27, 2011. FDA's draft guidance represents FDA's proposed approach on this topic. Web site addresses for all guidance documents referenced in this guidance can be found in Appendix A: List of References.

[4] 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.

Therefore, in order to find a new device SE to a predicate device, FDA must first find that the two devices have the "same intended use." FDA must then determine that the two devices have "the same technological characteristics," or that any differences in technological characteristics do 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)) as:

> 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 find the new device to be not substantially equivalent (NSE) to the predicate device. [5] On the other hand, if FDA determines that the different technological characteristics do not raise different questions of safety and effectiveness, FDA will then evaluate the technological differences between the new device and the predicate devices to determine their effect on safety and effectiveness (i.e., whether the new device is "as safe and effective" as the predicate device). 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] We believe the approach described in this draft guidance document would provide greater clarity regarding the factors that FDA considers in making substantial equivalence determinations when there are different technological characteristics between the new device and the predicate device that do not raise different questions of safety and effectiveness.

[5] *See* the proposed 510(k) Decision-Making Flowchart for the critical decision making points in the 510(k) review process, at Appendix A of the 510(k) Program draft guidance. FDA's draft guidance represents FDA's proposed approach on this topic.

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

B. Performance Data

When FDA is reviewing a new device that has different technological characteristics than the predicate device, performance data may be necessary to assess the safety and effectiveness of the new device as compared to the predicate device.[7] When evaluating the performance data, FDA may consider the risks and benefits of the new device in comparison to the predicate device before making a substantial equivalence determination. The type and quantity of performance data that may be necessary to support a determination of substantial equivalence depends upon the new device. Performance data may be generated from both non-clinical and clinical testing, and both non-clinical and clinical data can play a role in FDA's evaluation of benefits and risks. Both types of performance data can provide information relating to the benefit and risk factors discussed in this guidance.

FDA relies on valid scientific evidence[8] when evaluating benefits and risks, including when identifying "probable risks" and "probable benefits."[9] In general, a "probable risk" and a "probable benefit"' do not include purely theoretical risks and benefits, but rather are supported by valid scientific evidence. Generally, isolated case reports, random experience, reports lacking sufficient details to permit scientific evaluation, and unsubstantiated opinions are not regarded as valid scientific evidence to show the new device's safety or effectiveness in comparison to a predicate device. However, such information may be considered when identifying a device that has questionable safety and effectiveness.[10]

III. Scope

The 510(k) review standard (substantial equivalence of a new device to a legally marketed (predicate) device) does not require a new device to be identical to a predicate device. In certain circumstances, FDA may find a device with indications for use[11] or technological characteristics

[7] For further discussion on requests for performance data, see footnote 3.

[8] Clinical data provided in support of any marketing submission, including a 510(k) when those data are relevant to a substantial equivalence determination, should fit the definition of valid scientific evidence in 21 CFR 860.7(c)(2). Valid scientific evidence is defined as "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." (21 CFR 860.7(c)(2)).

[9] In general, "probable" and "probability" in this guidance have the same connotation as in 21 CFR 860.7(b)(3), i.e. they refer to the likelihood of the patient experiencing a benefit or risk. Hypothesis testing, formal concepts of probability and predictive probability, likelihood, etc., typically are critical elements in the assessment of "probable" benefit and risk. FDA does not intend for the use of the term "probable benefit" in this guidance to refer to the regulatory term 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.

[10] 21 CFR 860.7(c)(2).

[11] 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 only if 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, do not necessarily result in a new intended

that are different from those of the predicate device to be SE to the predicate device. This guidance document does not focus on the first step of the 510(k) review process where FDA must find that the intended use of the device and its predicate are "the same," but instead focuses on the step of the review process after FDA has determined that the new device and the predicate device have different technological characteristics and that the new device does not raise different questions of safety and effectiveness.[12] At this point in the review process, FDA must determine whether the new device is "as safe and effective" as the predicate device. The principal benefit and risk factors that FDA considers during this step in the 510(k) review process to assist in making a substantial equivalence determination are described below. We also provide examples of how these factors may be used during premarket review.

This guidance applies to both diagnostic and therapeutic devices. Not all the factors listed in this guidance will be applicable to each 510(k) submission.

For guidance on the benefit-risk factors considered in the review of PMAs or *de novo* classification requests, see the FDA Guidance, *Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approvals and De Novo Classifications*, issued on March 28, 2012 ("PMA and *De Novo* Guidance"). This draft guidance addresses benefit-risk factors similar to those in the PMA and *De Novo* Guidance, but, unlike the benefit-risk determinations during the premarket review process for PMA applications and *de novo* classification requests which do not require a comparison to any other device, in evaluating benefits and risks during a 510(k) premarket review, FDA considers the benefits and risks of the new device as compared to the predicate device.

IV. Benefit and Risk Factors

The benefit-risk factors explained below are the principal factors that FDA considers when reviewing performance data to evaluate whether the new device is as safe and effective as the predicate device, where there are different technological characteristics in the new device and FDA has determined that the differences in the technological characteristics do not raise different questions of safety and effectiveness. FDA may make a determination that the new device is SE to the predicate device even if there are differences in the benefits and risks of the new device. Although the degree of difference in the benefits and risks of the new device that FDA may find acceptable in a substantial equivalence decision will be assessed on a case-by-case basis, examples of how differences in benefit and risk of the new device may be evaluated as compared to the predicate device include:

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use. Such differences result in a new intended use when they affect (or may affect) the safety and/or effectiveness of the new device as compared to the predicate device and the differences cannot be adequately evaluated under the comparative standard of substantial equivalence. For more information on the processes associated with determining whether a new device with new indications for use has a new intended use, see footnote 3.

[12] See footnote 5.

Decreased Benefit/Decreased Risk: If there are different technological characteristics between the new device and the predicate device and FDA finds from a review of the submitted performance data that there are decreased benefits with the new device as compared to the predicate device, FDA may still determine that the new device is SE to the predicate device if, for example, there are also decreased risks with the new device as compared to the predicate device. When looking at the smaller benefits in the new device, FDA may consider the amount by which the benefit has decreased when determining whether the device is SE. Depending on the decrease in benefit of the new device as compared to the predicate device, FDA may determine that the new device is NSE to the predicate device, even despite decreased risks of the new device.

Increased Risk/Increased Benefit: If the risks associated with the new device increase as compared to the predicate device, FDA may still determine that the new device is SE to the predicate device if, for example, FDA finds from a review of the new device's performance data that there are also increased benefits with the new device as compared to the predicate device. When looking at the increased risks posed by the new device, FDA may consider the degree of risk in comparison to the predicate device. FDA may also consider whether additional measures may help mitigate the increased risks. Depending on the increase in risk of the new device as compared to the predicate device, FDA may determine that the new device is NSE to the predicate device, even despite increased benefits of the new device.

The factors described below may be considered during the course of FDA's review of the new device's performance data in a premarket submission. Not all factors may be applicable to each 510(k) submission. Each factor that is considered is in comparison to the predicate device.

A. Assessment of the Benefits of Devices

Extent of the probable benefit(s): FDA assesses information provided in a 510(k) submission concerning the extent of the probable benefit(s) by taking into account the following factors individually and in the aggregate as compared to the predicate device:

- **Type of benefit(s)** – examples include, but are not limited to, the device's impact on clinical management, patient health, and patient satisfaction in the target population, such as the effect on patient management and quality of life, probability of survival, improvement of patient function, prevention of loss of function, and relief from symptoms. These endpoints denoting clinical benefit are usually measured directly, but in some cases may be demonstrated by use of validated surrogate endpoints. For diagnostic devices, a benefit may be assessed in reference to the nature of the public health impact of a particular device due to its ability to identify a specific disease, provide diagnosis at different stages of a disease, predict future disease onset, and/or identify patients more likely to respond to a given therapy and therefore enable treatment of the disease or reduce/prevent its spread.

- **Magnitude of the benefit(s)** – we often assess benefit along a scale or according to specific endpoints or criteria (e.g., types of benefits), or by evaluating whether a pre-identified health threshold was achieved. The change in clinical study subjects' condition or clinical management as measured on that scale, or as shown by an improvement or worsening of the endpoint, is what allows us to assess the magnitude of the benefit in subjects. Absent explicit outcome data, 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. Variation in the magnitude of the benefit across a population may also be considered.

- **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, on the other hand, that a benefit may occur frequently in patients throughout the target population. Demonstration of a large benefit experienced by a small proportion of subjects may raise considerations that differ from those in instances where a small benefit is experienced by a large proportion of subjects.

- **Duration of effect(s)** (i.e., how long the benefit can be expected to last for the patient) – some treatments are 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's 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

Extent of the probable risk(s)/harm(s): FDA assesses the extent of the probable risk(s)/harm(s) by taking into account the following factors individually and in the aggregate:

- **Severity, types, number and rates[13] of harmful events associated with the use of the device:[14]**
    - **Device-related serious adverse events** – those events that may have been or were attributed to the use of the device and that cause or contribute to a death or an injury or illness that is life-threatening, results in permanent impairment or

[13] For purposes of this guidance, "rates" means the number of harmful events per patient or number of harmful events per unit of time.

[14] We have listed each type of harm individually for the purpose of clarifying which of the more commonly recognized harms FDA would consider in benefit-risk assessments. In making benefit-risk assessments, FDA may consider each type of harm individually and in the aggregate.

damage to the body, or requires medical or surgical intervention to prevent permanent harm to the body.[15]

- **Device-related non-serious adverse events** – those events that may have been or were attributed to the use of the device and that do not meet the criteria for classification as a device-related serious adverse event.
- **Procedure-related complications** – harms to the patient that would not be included under serious or non-serious adverse events, and that indirectly result 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.[16]

- **Probability of a harmful event** – the proportion of the intended population that would be expected to experience a harmful event. FDA would factor whether an event occurs once or repeatedly into the measurement of probability.

- **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, on the other hand, that a harmful event may occur frequently in patients throughout the target population.

- **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 would consider the severity of the harm along with its duration.

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

We also consider the number of different types of harmful events that can potentially result from using the device and the severity of their aggregate effect. When multiple harmful events occur at once, they have a greater aggregate effect. For example, there may be a harmful event that is

[15] See 21 CFR 803.3.

[16] This consideration affects the risk profile of in vitro diagnostic devices when the biological material is collected via an invasive procedure for the purpose of performing the diagnostic test.

considered minor when it occurs on its own, but, when it occurs along with other harmful events, the aggregate effect on the patient can be substantial.

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

Uncertainty – when determining if a new device is as safe and effective as a predicate device, we consider the degree of certainty of the benefits and risks of a 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 unreliable and may not provide the degree of information necessary to fully understand the effects of the new technology. Additionally, for certain device types, it is sometimes difficult to distinguish between a real effect and a placebo effect in the absence of a design that is capable of blinding investigators and subjects. Furthermore, repeatability of the study results, validation of the analytical approach, and results of other similar studies can all influence the level of certainty.

Characterization of the disease/condition – the treated or diagnosed disease/condition, its clinical manifestation, how it affects the patients who have it, 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) are all important factors that FDA considers when evaluating the benefits and risks of the new device.

Patient tolerance for risk and perspective on benefit – risk tolerance varies among patients, and affects individual patient's 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 a patient-centric assessment 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 should take into account both the patients' willingness and unwillingness to use a device or tolerate risk when evaluating the relative safety and efficacy of the new device. FDA may also consider evidence relating to patients' perspective on what constitutes a meaningful benefit, as some set of patients may value a benefit more than others. Assessing patient tolerance for risk and perspective on benefit may be an informative and helpful factor in evaluating the overall benefit-risk profile of a device and whether a device is as safe and effective as a predicate. For example, inconvenience or discomfort may reduce patient compliance with instructions for use, which could result in lower effectiveness. FDA recommends that any submitter who is considering developing or presenting valid measurement

methods and/or data concerning patient risk tolerance or perspective on benefit in its 510(k) submission have early interaction with the appropriate FDA review division.[17]

Benefit for the healthcare professional 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 healthcare professionals or caregivers by improving the way they care for the patients and consequently improving patient outcomes. Examples could include 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 healthcare 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 healthcare professionals or caregivers in the submitter's 510(k) submission have early interaction with the appropriate FDA review division.[18]

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, 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 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.

Postmarket data – the use of devices in a postmarket setting provides 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 any 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 regarding the benefits and risks when evaluating benefits and risks of the new device in accordance with a substantial equivalence 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,[19] and may order postmarket surveillance for a new device that is expected to have significant use in pediatric populations as a condition to a substantial

[17] See FDA's Guidance, *Medical Devices: The Pre-Submission Program and Meetings with Food and Drug Administration Staff*, issued on February 18, 2014, which provides a mechanism for FDA to provide advice to submitters during the developmental stage of certain submissions to FDA, including 510(k) submissions.
[18] See id.
[19] Section 522 of the FD&C Act (21 U.S.C. § 360l).

equivalence determination.[20] 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) submissions, 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 FDA's guidance, "*The Least Burdensome Provisions of the FDA Modernization Act of 1997: Concept and Principles*," issued October 4, 2002, 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 the premarket data for 510(k) submissions, while still ensuring the safety and effectiveness of the device. In some cases, FDA may accept a greater degree of premarket uncertainty regarding a device's benefit-risk profile through a greater reliance on postmarket controls, such as postmarket surveillance where applicable, in order to reduce the premarket burden for a 510(k) submission, if FDA's overall assessment is sufficiently balanced by other factors to support substantial equivalence and taking into account FDA's limitations with respect to requiring postmarket studies for 510(k)s.

Innovative technology – When a new device has technological improvements that are important for public health, we may accept greater uncertainty in an assessment of benefits and risks as compared to the predicate device than for most 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 SE to the predicate device. Innovative changes are evaluated on a case-by-case basis in terms of the degree of the advantage.

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 treatment of the benefit-risk issues associated with any actual 510(k) submission. 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 considers the factors described in this guidance when evaluating benefits and risks during a 510(k) 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.

Example 1

[20] Section 522(a)(1)(B) of the FD&C Act (21 U.S.C. § 360l(a)(1)(B)).

A manufacturer submits a 510(k) for a manual 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 additional risk because the new cutting action exposes additional anatomy of the patient to an increased potential for 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 notes that the bench testing was not designed to address the additional, increased risk. The manufacturer provides animal and clinical performance data to demonstrate that the risks noted by the review team had very low incidence. In a clinical study that makes 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 and therefore reducing the likelihood of injury to neighboring tissue when accessing the difficult to reach anatomical areas in the patient. The device is available in a range of sizes, which raises concern about elevated risk if larger sizes than necessary are used because this resulted in higher adverse event rates in the animal study.

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 clinical 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 provides animal and clinical data to address the potential 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 Healthcare Professional or Caregiver: The new design allowed for easier use by the surgeons as demonstrated in the survey data provided by the manufacturer, thereby reducing risk of injury to the patient.

Substantial Equivalence Analysis: The predicate and the new device have the same intended use, and FDA determined that the technological differences do not raise different questions of safety and effectiveness. However, these technological differences may impact the safety and

effectiveness of the new device. Specifically, the technical difficulties present an increased risk of injury to the dura, arteries, veins, and nerve roots. The manufacturer provides animal and clinical data to address these potential harms and 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 potential risk may be slightly higher than that of the predicate due to the nature of cutting, the increase was demonstrated to be minimal. In addition, the 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 may have a comparable benefit-risk profile for the indicated patient population to the predicate device, this device would likely be found SE.

Example 2

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 that has been shown to produce different photobiological effects, has a power level much lower than the predicate device, and has a constant energy delivery sequence versus the pulsing sequence of the predicate device. For the treatment of onychomycosis, the purported mechanism of action is either a photobiological process in which the laser wavelength interacts with some chromophore 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 mechanism of action between the new device and predicate device, the manufacturer provides clinical data to evaluate the effectiveness of the device. The device would be deemed as effective 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 device is considered to pose a lower risk than the predicate because the power level of the device is significantly less.

Benefits: The new device offers an easier treatment modality than the predicate device. However, the study failed to meet the primary endpoint, that is, 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 trial raise significant concerns regarding the reliability of the observed benefit of the new device. The proportion of responders is lower than desired. In

addition, there are significant data inconsistencies regarding the manufacturer's photographs and data set.

Substantial Equivalence Analysis: The new device has the same intended use as the predicate device. However, there are technological differences between the new device and the predicate device. Although these technological differences do not raise different questions of safety and effectiveness as compared to the predicate device, the differences may affect the safety and effectiveness of the new device. Due to the differences in technological characteristics between the new device and predicate device, the manufacturer provides clinical data to establish substantial equivalence. The clinical data fails to demonstrate clinically meaningful benefit. In addition, the provided data presents significant inconsistencies and is not reliable. Although new device is less risky, the benefit of the device is much smaller than the predicate device. Additionally, there is a high degree of uncertainty with the small benefit observed. Therefore, the new device may not have a comparable benefit-risk profile to the predicate device and a NSE decision may be given.

Example 3

A manufacturer submits a 510(k) for an external infusion pump that can be used in an ambulatory, portable setting. The device manufacturer claims substantial equivalence to a stand-alone 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.[21]

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 (e.g., impact, vibration, etc.), fluid ingress, pressure altitude, and

[21] 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 FDA's Guidance, *Emergency Use Authorization of Medical Products*, issued in July 2007. 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.

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.

Benefits: Compared to the predicate device, the compact, portable platform of the new device enables the healthcare professional to extend 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 healthcare 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 healthcare 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 disasters.

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

Additional Factors:

Benefit for the Healthcare Professional or Caregiver: The predicate device does not allow the healthcare professional to extend IV therapy into the mobile setting. This new device allows healthcare 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.

Substantial Equivalence Analysis: The new device and the predicate device have the same intended use – to deliver fluids to a patient in a controlled manner. However, the new device, unlike the predicate device, is fully battery-operated, compact, and contains a simplified user interface so that it can be used in a mobile ambulatory setting. These differences, especially the use of the device in an ambulatory setting, represent different technological characteristics that may affect the safety and effectiveness of the device. The higher risk of damage-related

malfunction in the ambulatory environment could result in under-infusion, over-infusion, or delay of therapy. These are not new questions of safety and effectiveness as damage-related malfunction to the predicate device is also possible. The manufacturer provided bench 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 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 may have a comparable benefit-risk profile for the indicated patient population to the predicate device, and so this device may be found SE.

Example 4

The manufacturer of a male condom composed of synthetic material claims substantial equivalence to a natural rubber latex condom. The only difference between the two devices is the material, synthetic versus natural rubber latex. There is concern that the new material may not perform as well as the 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). The new device would need to demonstrate non-inferiority to natural rubber latex condoms for a co-primary endpoint evaluating slippage and breakage during sexual intercourse. The manufacturer performed the clinical study, but the device missed one of the endpoints in the co-primary endpoint.

Benefits: This device provides another option for contraception and prophylaxis, which is particularly beneficial for users and their partners 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 a lower rate of breakage for the synthetic condoms compared to natural rubber latex condoms, but the slippage rate was slightly higher.

Additional Factors:

Risk Mitigation: To mitigate the risk of slippage revealed by the clinical study, a warning is placed on all labeling that states that the device should be used only if the user has an allergy to latex.

Substantial Equivalence Analysis: The new device and the predicate device have the same intended use - for contraception and prophylaxis. However, the new device is composed of a different material than that of the predicate, which represents a different technological characteristic. Although this technological difference does not raise different types of safety and

effectiveness questions as compared to the predicate device, this difference may affect the safety and effectiveness of the new device. 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 increase slippage during sexual intercourse, resulting in an increased risk of undesired pregnancy and transmission of STIs. These risks were evaluated in a clinical study and the results from the clinical study showed that the new device decreased breakage, but there was an increase in slippage. This increase in slippage rate between the new condom and the predicate condom is partially mitigated by warnings on the labeling. Additionally, the new condom is non-inferior to the predicate condom based upon a combined rate of failure (slippage and breakage). 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 may have a comparable benefit-risk profile for the indicated patient population to the predicate device. This device may be found SE.

Example 5

A device that exerts pressure on the mouth is used to treat obstructive sleep apnea in adults. In comparison to the predicate device, the gold standard first line treatment for this condition, the new device has a different mechanism of action to achieve the same intended therapeutic outcome. There is concern that the new mechanism of action 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 provides 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 is provided. The study results show that the new device had a clinically meaningful reduction in AHI. Although clinically meaningful, the reduction in AHI demonstrated by the new device is less than that of the predicate device. On the other hand, the new device scored significantly higher on a patient satisfaction questionnaire as compared to the predicate device.

Benefits: Although the new device provides less benefit in terms of AHI reduction as compared to the predicate, the improvement is still clinically meaningful. Additionally, as the patient satisfaction data from the clinical data indicated, the design of the new device introduces features that make it easier to use and more comfortable to wear compared to the predicate device. These new features may increase overall patient compliance as compared to the predicate device, which is not well-tolerated by patients.

Risks: As demonstrated by the bench performance data, there is a risk that the level of pressure exerted could potentially partially close the oral cavity from the breathing mechanism, thereby restricting the patient to breathing exclusively from the nose. Because an alternative airway would theoretically not be available to a patient using the new device, the buildup of mucus or

acute inflammation in the nose may cause a partial airway obstruction during sleep, thereby restricting the user to breathing through the nose.

Additional Factors:

Uncertainty: The clinical study design provided was not optimally designed to demonstrate safety and effectiveness. A large number of screened subjects were lost to follow-up and the submitter did not provide effectiveness data for them. Additionally, the 28-day study duration may not be optimal to determine durability of the effect for the treatment of sleep apnea.

Patient Tolerance for Risk and Perspective on Benefit: The predicate device is currently recognized as the gold standard first-line treatment of obstructive sleep apnea, but is not well-tolerated by all prospective patients. Because the new device is more comfortable to wear and easier to use, patients may be willing to tolerate less of a reduction in AHI.

Innovative Technology**:** The technology uses a new mechanism for the treatment of obstructive sleep apnea that is better tolerated by patients than the predicate device.

Substantial Equivalence Analysis: The new device and the predicate device have the same intended use - for treatment of obstructive sleep apnea. However, the new device contains new technological characteristics that, although not raising new questions of safety and effectiveness, may affect the safety and effectiveness of the device. The new design features resulted in higher patient satisfaction, and thereby may increase patient compliance compared to a predicate device. However, there will be less of a reduction in AHI in patients who use the new device. Moreover, patients may be willing to tolerate a slightly higher AHI compared to the current gold standard, the predicate device, if the new device is more comfortable to wear and easier to use than the predicate device. Because the increase in risk that the new mechanism of action could potentially partially close the oral cavity is accompanied by an increase in benefit, the benefit-risk profile of new device for the indicated patient population may be comparable to the predicate device. This device may be found SE.

Example 6

The manufacturer of a new test for measurement of prothrombin time (PT) international normalized ratio (INR) and coagulation factor levels obtains 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 show positive bias, compared to results from the predicate device. INR results from the two devices are in better agreement across the measurement range, but include few samples with markedly elevated INR. Calibrated assays for fibrinogen and coagulation factors II, V, VII and X show strong correlation between the new assay and the predicate assay, though times required for clot formation at low factor levels are longer with the new device than with the predicate device. Precision and inter-day/inter-lot studies show that results from the new device are more reproducible than are results from the

predicate device. Studies of known PT interferents, at physiologically relevant concentrations, show no unexpected effect on results from the new assay. Review of recent postmarket medical device reports (MDR) for PT devices shows that the only previously cleared PT product incorporating a (different) recombinant DNA reagent is subject to interference from an antibiotic 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 show no interference with the new product by the antibiotic associated with the MDRs or by currently marketed members of that antibiotic's class.

Benefits: The new test provides the benefits expected from all members of its class, detecting combined or single factor deficiencies of the extrinsic coagulation pathway with implications for patients' management. The better reproducibility of results from the new test suggests that the frequency of falsely high, low or normal results (at least within the typically observed range of results) will be decreased with the new test compared to the predicate test.

Risks: There are no new risks identified for the new device compared to the predicate device.

Additional Factors:

Uncertainty: The degree of result differences (between new and predicate tests) at extreme INR values is not fully evaluated. Optimal management might differ for patients with extreme values from the new device versus the predicate device. In addition, the effects of unexamined interferents might differ between the new device and the predicate device.

Risk Mitigation: Risks attributable to the PT/INR testing are largely mitigated through expertise and procedures of the laboratories that are certified to perform PT/INR and coagulation factor testing. Markedly abnormal or unexpected test results are subject to confirmation and investigation by the testing laboratory. Prolonged raw clotting times are placed in clinical context by the laboratories' experience with coagulation tests, and the use of INR and % activity for results reporting decreases reliance on raw clotting times for patients' management.

Postmarket Data: Postmarket controls could mitigate the risks associated with the premarket uncertainty regarding novel interferences for this device.

Substantial Equivalence Analysis: The new device has the same intended use as the predicate device, but there are technological differences between the new device and the predicate device. Although these technological differences do not raise different questions of safety and effectiveness as compared to the predicate device, the differences may affect the safety and effectiveness of the new device. However, with comparable analytical performance (as normalized) based on available studies, and with risk mitigation that is well-established and effective in the face of uncertainties identified for the new technology, the benefit-risk profiles of the new device and the predicate device are similar. Therefore, the device may be found SE.

Example 7

A manufacturer of menstrual tampon composed of a new synthetic wadding material claims substantial equivalence to a menstrual tampon composed of a different synthetic material, rayon. The new wadding material has the ability to absorb the same amount of menstrual blood as the predicate device, but with less physical expansion of the wadding. There is concern that the new material may enhance the growth of Staphylococcus aureus (*S. aureus*) and increase the production of toxic shock syndrome toxin-1 (TSST-1). The manufacturer provides toxicology data to demonstrate that the tampon does not enhance the growth of *S. aureus*, increase the production of TSST-1, or alter the growth of normal vaginal microflora. However, the data submitted by the manufacturer revealed anomalies in the microbiological testing that call into question the results. In a response to FDA's request to explain the anomalies, the submitter repeated the microbiological testing, revealing several inconsistencies in the data.

Benefits: The ability of the new material to absorb the same amount of fluid, but with less physical expansion could increase comfort for patients using tampons.

Risks: Given the anomalies in the microbiological testing, there is a possibility that the new material enhances the growth of *S. aureus* and alters the growth of normal vaginal microflora. This microbiological testing is important to demonstrate that the tampon does not allow *S. aureus* to outcompete the normal vaginal microflora. Overgrowth of *S. aureus* can lead to TSS, a potentially fatal disease caused by the production of staphylococcal toxins. In addition, the inconsistencies in the data shed doubt regarding the validity of the results.

Additional Factors:

Uncertainty: The results of the microbiological testing raise significant concerns regarding safety. The testing provided by the manufacturer revealed several anomalies in the results.

Substantial Equivalence Analysis: The intended use of the new device and the predicate device are the same—both are inserted into the vagina to absorb menstrual blood. However, the new device is composed of a different synthetic wadding material. The new material represents different technological characteristics not found in the predicate that may affect the safety and effectiveness by enhancing the growth of *S. aureus*, increasing the production of TSST-1, and/or altering the growth of the normal vaginal microflora. However, this is not a different question of safety and effectiveness, as all manufacturers of tampons must demonstrate that their device does not enhance the growth of *S. aureus*. The manufacturer provided data from microbiological testing performed on the new device that contained anomalies in the data; repeat testing of the device revealed several inconsistencies in the data that indicated the device may enhance the growth of *S. aureus*. Overgrowth of *S. aureus* can lead to TSS, a potentially fatal disease. Therefore, although the new tampon may be more comfortable to wear compared to the predicate device, there is too much uncertainty regarding the increased risk of developing TSS as compared to the predicate device, such that the benefit-risk profiles of the new device and predicate may not be comparable. Therefore, the device may be found NSE.

Appendix A: List of References

For the most recent version of a CDRH guidance, check the CDRH guidance web page at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/default.htm.

1. *The 510(k)Program: Evaluating Substantial Equivalence in Premarket Notifications [510(k)]; Draft Guidance for Industry and Food and Drug Administration Staff* (December 27, 2011). Available at: http://www.fda.gov/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm282958.htm.

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5. *Emergency Use Authorization of Medical Products Guidance* (July 2007). Available at: http://www.fda.gov/RegulatoryInformation/Guidances/ucm125127.htm.