Factors to Consider Regarding Benefit-Risk in Medical Device Product Availability, Compliance, and Enforcement Decisions

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Draft Guidance for Industry and Food and Drug Administration Staff

DRAFT GUIDANCE

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Document issued on June 16, 2016.

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

Preface

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Draft Guidance for Industry and Food and Drug Administration Staff

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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

I. Introduction

FDA has developed this draft guidance document to provide clarity for FDA staff and industry regarding the benefit and risk factors FDA may consider in prioritizing resources for compliance and enforcement efforts to maximize medical device quality[1] and patient safety. This draft guidance is not intended to limit FDA action; rather, it describes the general framework for medical device decision making in the product availability, compliance, and enforcement arenas. Product availability and other medical device compliance and enforcement decisions are generally fact-specific. However, FDA believes that explaining how we consider the factors listed in this draft guidance document will improve the consistency and transparency of these kinds of decisions. A common understanding of how FDA considers benefit and risk may better align industry's and FDA's focus on actions that maximize benefit to patients, improve medical device quality, and reduce risk to patients.

This draft guidance, when finalized, is intended to provide a framework for FDA and stakeholders that sets forth overarching benefit-risk principles. FDA may consider the types of benefit-risk factors described in this draft guidance—including reliable patient preference information from a representative sample—on a case-by-case basis when determining the appropriate actions to take and to help ensure that informed and science-based decisions are made to the greatest extent

[1] "*Quality* means the totality of features and characteristics that bear on the ability of a device to satisfy fitness-for-use, including safety and performance." 21 CFR 820.3(s).

practicable. Factors may be weighted differently for different types of decisions and as the timeframe allows. FDA intends to use pilots to help determine how to apply the benefit-risk framework described in this draft guidance.

In addition, this draft guidance, when finalized, is intended to harmonize FDA's approach to weighing benefits and risks for medical device product availability, compliance, and enforcement decisions with FDA's benefit-risk framework for assessing medical device marketing and investigational device exemption (IDE) applications. The benefit-risk factors in this draft guidance also support assessment of medical devices with real world evidence. While the benefit-risk factors in this draft guidance are not identical to the other frameworks, this draft guidance builds upon FDA's premarket review benefit-risk policy in an effort to improve consistency in our patient centered approach and decision making across the total product life cycle. This draft guidance is intended to complement, not supplant, FDA's "Guidance for Industry and Food and Drug Administration Staff - Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approvals and De Novo Classifications."

For the current edition of the FDA-recognized standard(s) referenced in this document, see the FDA Recognized Consensus Standards Database Web site at http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/search.cfm.

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. Scope

The framework described in this draft guidance may be applicable to both industry and FDA decisions. The benefit-risk factors may be considered when device manufacturers evaluate appropriate responses to nonconforming product or regulatory compliance issues, such as determining whether to limit the availability of a medical device (e.g., a voluntary recall or market withdrawal). FDA may consider the benefit-risk factors during, for example, evaluation of device shortage situations, selection of the appropriate regulatory engagement mechanism following an inspection during which regulatory non-compliance was observed, evaluation of recalls, and consideration of petitions for variance from those sections of the Quality System (QS) regulation (21 CFR part 820) for which there were inspectional observations during a Premarket Approval (PMA) pre-approval inspection. Premarket submission review decisions, such as premarket notification (510(k)) substantial equivalence determinations, de novo classification, and PMA, Humanitarian Device Exemption (HDE) or IDE application approval decisions, are beyond the scope of this draft guidance.

Because of the potentially direct effect on patients, medical device compliance and enforcement decisions that affect product availability should generally include consideration of specific factors. The factors described in this document can apply to many situations where the Agency or manufacturer has information that leads to quality, compliance, or other concerns regarding a medical device and considers taking action that could have a direct effect on the device's

availability. These situations may include information about new risks or about known risks occurring at greater than expected frequency or severity. To support a common understanding of other kinds of compliance and enforcement decision making, the factors in this draft guidance may also be considered when the Agency or manufacturer considers taking action that is unlikely to directly affect product availability but seeks to minimize risks to patients associated with manufacturer quality and regulatory compliance issues (e.g., issues in design, manufacturing, or reporting related to the device), while also considering the benefits patients may receive from the device. The intersection of this draft guidance with ISO 14971: *Medical devices – Application of risk management to medical devices*[2] is discussed in Appendix A.

This draft guidance applies to both diagnostic and therapeutic medical devices subject to, and exempt from, premarket review. The scope of this draft guidance excludes medical devices regulated by FDA's Center for Biologics Evaluation and Research (CBER); combination products, as defined in 21 CFR 3.2(e), for which CDRH is not the lead Center; and electronic products that are not devices as defined in section 201(h) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), as regulated by CDRH under the Electronic Product Radiation Control (ERPC) provisions in the FD&C Act and implementing regulations (21 CFR Subchapter J−Radiological Health). This draft guidance also does not apply to products (e.g., drugs, biologics, dietary supplements, foods, tobacco products, or cosmetics) regulated by other FDA Centers.

Guidance documents, including this draft guidance, are not binding, and the concepts and factors described herein generally explain how benefit-risk assessments can be made. This draft guidance does not preclude FDA from taking regulatory or other action in response to a violation of applicable law or regulation.

III. Patient[3] Focused Benefit-Risk Assessments for Medical Device Product Availability, Compliance, and Enforcement Decisions

FDA has authority to limit the availability of violative medical devices and to pursue other compliance and enforcement actions related to violative medical devices. FDA recognizes that, to achieve the Agency's goal of protecting and promoting the public health, decisions regarding these actions should be made while focusing on the impact on patients. Failure to consider the short-term and long-term impact of non-compliance on the benefit-risk profile of the device and the benefit-risk tradeoffs of FDA's decision options on the health and quality of life of patients could result in regulatory actions with unintended adverse effects (e.g., shortage of medically necessary devices).

In certain situations involving risks of patient harm, FDA and industry, individually or collaboratively, can help maximize benefit and reduce risk to patients by assessing the situation, considering patients' perspectives, evaluating any regulatory non-compliance or device

[2] For the current edition of the FDA-recognized standard(s) referenced in this document, see the FDA Recognized Consensus Standards Database Web site at http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/search.cfm.

[3] Although this draft guidance focuses on patients, when relevant, the benefit-risk factors also take into account benefits or risks for non-patient users of medical devices, such as healthcare providers and caregivers.

nonconformity in light of the benefit-risk profile of the device,[4] factoring in alternatives, where available, considering the benefit-risk tradeoffs for patients of each decision option, and determining the most appropriate next steps.

When FDA is working with a manufacturer to address a failure to comply with applicable statutes or regulations, observed unanticipated harm to patients or users, or identified device nonconformities, FDA strives to be clear with that manufacturer about the benefits and risks the Agency is considering. As with premarket review decisions, when making medical device product availability, compliance, and enforcement decisions informed by benefit-risk, FDA may consider relevant, reliable information relating to patient perspectives on what constitutes meaningful benefit, what constitutes risk, and what tradeoffs patients are willing to accept, if such information is available at the time of decision, as well as what alternatives are available. Before arriving at a decision, FDA may also consider the manufacturer's approach to minimize harm or to mitigate the increased risks that result from regulatory non-compliance or nonconformity of the product, their compliance history, and the scope of the issue.

By providing greater clarity about the factors we consider, we intend to improve consistency and transparency and to better align industry's and FDA's focus on actions that maximize benefit to patients, improve medical device quality, and reduce risk to patients. In Appendices B, C, and D, draft benefit-risk assessment worksheets have been provided to support consideration of the factors by FDA staff and industry.

Note that as with premarket benefit-risk determinations made when evaluating marketing and IDE applications, benefit-risk assessments made in product availability, compliance, and enforcement contexts may change over time. For example, as the practice of medicine evolves, clinical experience increases, or additional treatment options become available to patients, a benefit-risk conclusion may change.

IV. Description of Factors to Consider Regarding Benefit-Risk for Medical Device Product Availability, Compliance, and Enforcement Decisions

In assessing benefit-risk factors for purposes of medical device product availability, compliance, and enforcement decisions, FDA considers relevant and reliable evidence and data available to the Agency at the time of a decision—including reliable patient preference information from a representative sample— on a case-by-case basis, to help ensure that informed and science-based decisions are made to the greatest extent practicable. FDA may use available evidence or request data to assess these factors, as appropriate. The benefit-risk assessments covered in this draft guidance document may compare the benefits and risks identified based on currently available

[4] "*Nonconformity* means the nonfulfillment of a specified requirement." 21 CFR 820.3(q).
In the preamble to the final rule for the QS regulation, "FDA emphasizes that a 'nonconformity' may not always rise to the level of a product defect or failure, but a product defect or failure will typically constitute a nonconformity." (61 FR 52610.)

information to those benefits and risks that were identified during premarket review benefit-risk assessments (or early risk assessments documented as part of a manufacturer's risk management process) in order to understand whether there has been a change in the benefit-risk analysis over time. We generally consider our device benefit-risk assessment along with data/information related to benefit-risk factors outlined in the draft guidance to reach our judgment about how to proceed in each situation.

A. Factors for the Assessment of Medical Device Benefits

When prioritizing compliance and enforcement efforts to maximize medical device quality and patient safety, FDA may assess the extent of benefit of a device by considering factors such as those listed below. The following factors, when relevant, should be considered in the aggregate. The factors may be considered early in the medical device product life cycle and reassessed as the device is used more widely.

Benefit, as described by the potential benefit factors, may change over time. The text below describes each factor for the purposes of this draft guidance and provides examples of how each factor may be considered.

Type of benefit(s) includes, but is not limited to, the medical device's impact on patient health and clinical management. Examples include the effect of the device on patient treatment plans and quality of life; impact on survival; and how much the medical device can aid in improving patient function, preventing loss of function, or providing relief from the symptoms of the disease or condition that the medical device is intended to treat.

As a medical device is used, clinicians may find unanticipated ways to use the medical device and additional types of benefit. For example, a surgical tool may be cleared for use in hernia repair surgery. Surgeons may find additional uses for the surgical tool that may lead to clearance of new uses, thus increasing the types of benefit.

Magnitude of benefit(s) is the degree to which patients experience the treatment benefit or the effectiveness of the medical device. The change in patients' conditions or the change in necessary clinical management may allow FDA to determine the magnitude of the benefit. Magnitude of benefit may be assessed against standards of care and expected performance and may change over time.

Likelihood of patients experiencing one or more benefits is the likelihood that the medical device will effectively treat or diagnose the patient's disease or condition. A medical device may not provide effective treatment or diagnosis for all patients. One method of determining the likelihood of benefit, for a particular patient population, is to determine the number of patients treated effectively and divide this by the total number of patients treated.

In assessing benefit, FDA may consider whether there are subpopulations included in the indication for use that are more likely to retain expected benefits than the overall population. If the subgroups can be identified, the likelihood of those patients experiencing benefit from the device may increase. The benefit for a subpopulation may also be greater than for the population as a whole, and this greater benefit should be considered in the overall benefit-risk assessment.

Duration of effects is how long the benefit can be expected to last for the patient. Curative treatments may be seen as providing higher benefit because of a longer duration of effect.

Knowledge of the duration of treatment effect may change as the medical device is used. For example, a medical device may have been approved with clinical endpoint data demonstrating effectiveness for 6 months. As the medical device is used, patients may experience significantly longer treatment effects than those described in the device labeling.

Patient preference on benefit is the value that patients place on use of the medical device. Faced with a severe or chronic disease, a patient may highly value the benefit provided by a medical device in light of the specific condition that patient has. For example, patients dying of congestive heart failure may highly value a medical device that extends their lives for a few months. Patients with less severe or chronic diseases may or may not place the same value on a device with a short-term benefit.

Benefit factors for healthcare professionals or caregivers include the benefit that healthcare professionals or caregivers experience by improving the way they care for patients, whether this directly improves patient outcomes or improves clinical practice. FDA recognizes that certain devices, such as surgical tools that allow different techniques or devices that positively affect ongoing patient management, may improve the benefit profile.

Medical necessity should be considered if a medical device provides benefits or addresses needs unmet by other medical devices or therapies. Benefit considerations should include an assessment of whether another medical device or therapy could be used in substitution, and the availability of that other medical device or therapy.

B. Factors for the Assessment of Medical Device Risks

When prioritizing compliance and enforcement efforts to maximize medical device quality and patient safety, FDA may assess the risk that a medical device will cause patient direct or indirect harm by considering factors such as those listed below. The following factors, when relevant, should be considered in aggregate. Each factor may be considered early in the medical device product life cycle and reassessed as the device is used more widely. Changes in risk should be noted in the manufacturer's risk management documentation. Changes in risk may occur due to, among other things, observed unanticipated harm to patients exposed to the device or to device users, changes in the medical device use environment, identified medical device nonconformities, and issues related to the design or manufacturing of the device. It should be noted that all devices have some level of anticipated risk, even without device nonconformities or regulatory non-compliance.

Medical device nonconformities may directly increase risk or introduce new risks. Failure to comply with applicable statutes or regulations also may be a negative indicator of a manufacturer's ability to consistently manufacture high quality medical devices, even if a device made by such a manufacturer still performs as expected. Postmarket data may also show that risk is higher than anticipated, even in the absence of a medical device nonconformity or regulatory non-compliance. Therefore, the risk factors listed below take into account considerations related to nonconforming

devices, failure to comply with applicable statutes or regulations, and harm potentially unrelated to compliance with legal requirements or device nonconformities.

Risk, as described by the potential risk factors, may change over time. The text below describes each risk factor for purposes of this draft guidance and provides examples of how the risk factor may be considered.

Risk severity is categorized into three levels and includes a duration component. The three levels are medical device-related deaths or serious injuries, medical device-related non-serious adverse events, and medical device-related events without reported harm.

Medical device-related deaths and serious injuries include those events (including procedure related complications) that may have been or were attributed to the use of the medical device and that cause or contribute to a death or injury or illness that is life-threatening, results in permanent impairment or damage to the body, or requires medical or surgical intervention to prevent permanent harm to the body.

Medical device-related non-serious adverse events include those events (including procedure related complications) that may have been or were attributed to the use of the medical device and that cause or contribute to minor, temporary or medically reversible injuries that do not meet the criteria for classification as a medical device-related serious injury.

Medical device-related events without reported harm can include medical device nonconformities which have no related harm, medical device malfunctions which have no related harm, procedure related complications with no related harm, and instances where a nonconformity or regulatory noncompliance was observed at the medical device manufacturing facility and no defective devices were released to the market. A medical device nonconformity can include the failure of a medical device to meet its performance specifications even though the device still performs adequately to meet the needs of a given patient.

Duration of harm to patient - Depending on circumstance, medical devices can cause harm to patients that is temporary, repeated but reversible, or permanent.

Likelihood of risk considers three risk factors related to the potential number of patients at risk of experiencing harm: the likelihood that a medical device will have problems, the likelihood of a patient experiencing harm, and the total number of patients exposed.

Likelihood of medical device nonconformity is the likelihood that the medical device will exhibit a specific failure mode or defect. Regulatory non-compliance may increase the likelihood of a medical device nonconformity. One method of calculating the likelihood of medical device nonconformity is to identify the number of nonconforming medical devices and divide by the total number of medical devices manufactured, under the same conditions.

Likelihood of a harmful event given exposure to a nonconforming device is the proportion of the intended population treated with or diagnosed by the nonconforming medical device that

would be expected to experience a harmful event if exposed to a nonconforming device. One method to calculate this likelihood is to take the number of patients treated with a nonconforming medical device and harmed and to divide by the total number of patients treated with nonconforming devices, over a similar time period, if reliable data exist.

The likelihood of a harmful event given exposure to a nonconforming device should be compared to the likelihood of a harmful event given exposure to a conforming device.

Number of patients exposed is the number of patients exposed to a nonconforming medical device or to a medical device manufactured by a noncompliant manufacturer.

Nonconforming product risks include whether nonconforming product has been distributed and if so, how many nonconforming devices are on the market.

Duration of exposure to population is the length of time between initial patient exposure to the device with the identified risk of harm and the point at which the risk of harm is successfully addressed.

False-positive or false-negative results are important risk factors for diagnostics. If a diagnostic medical device gives a false-positive result, the patient might, for example, be incorrectly diagnosed with a serious disease and receive an unnecessary treatment, incurring all the risks that accompany that treatment. If a diagnostic medical device gives a false-negative result, the patient might not be diagnosed with the correct disease or condition and might not receive an effective treatment (thereby missing out on the benefits that treatment would confer). The risks associated with false positives and false negatives can be multifold, but are considered by FDA in light of probable risks.

Patient tolerance of risk is the concern that patients have regarding harm or potential harm caused by the device. Patient tolerance of risk may take into account both the patients' willingness and unwillingness to use a nonconforming medical device, to use a device manufactured by a non-compliant manufacturer, or to tolerate harm (both probable and actual). Risk tolerance varies among patients, and affects individual patients' decisions as to whether risks associated with the medical device's technology are acceptable in exchange for the benefit. Risk tolerance may also vary with risk severity (e.g., there may be special subpopulations in which risk severity is higher). Patients may not understand device-related risks for all types of devices (e.g., lack of FDA review, certain diagnostics). For prescription devices, a patient's assessment of risk would be appropriately informed by information from his or her clinician.

Risk factors for healthcare professionals or caregivers may be considered when the risk may have an adverse impact on the clinician or caregiver.

C. Additional Benefit-Risk Factors to Consider When Making Product Availability, Compliance, and Enforcement Decisions

In addition to the benefit-risk factors described above, FDA may consider additional important benefit-risk factors related to product availability, compliance, and enforcement decisions, such as

those listed below. The text below describes additional factors. Section V provides examples of how all the factors may be considered in specific situations.

Uncertainty is an important factor, since at any point in the total product life cycle, there is never 100% certainty regarding the safety, effectiveness, or quality of a device. However, the degree of certainty of the benefits and risks of a device is a factor FDA considers when making benefit-risk assessments.

Mitigations are actions taken by the manufacturer, by FDA, or by other stakeholders to recover benefit, to limit risk from nonconforming product, to address underlying QS problems, or to limit harm. Mitigations could address, among other considerations, as applicable: clinical practice; use errors; unmet medical needs; the use environment; user population; user skill level; clinical understanding in assessing risk; current expectations in clinical use; any changes in medical practice, e.g., standard of care, that could increase risk; and use in emergency/crisis situations.

Detectability refers to whether a nonconformity could be identified, either by the manufacturer or by the user. A nonconformity which can be identified prior to use of the device may harm fewer patients than a nonconformity which is not identified prior to use. A detected nonconforming device may still cause patient harm (e.g., a mislabeled orthopedic implant may cause a delay in surgery). Time between exposure to a nonconforming device and symptoms can increase the frequency of harm because it can take longer to determine the cause of the harm, making it likely that patients will be exposed to the device in the intervening time.

Failure mode is the specific method or type of failure. The failure mode may be used to identify the cause of the nonconformance including whether the nonconformance is related to manufacturing, design, use conditions, or environment.

Scope of the device issue should be evaluated to assess whether the risks identified are potentially inherent to similar devices of this type (i.e., whether the risk is specific to a single device, a single manufacturer, or is industry wide).

Patient impact is the impact on the health and quality of life of patients if a particular compliance or enforcement action is, or is not, taken or if the device relevant to the nonconformity or regulatory non-compliance is not available. FDA and, where appropriate, industry should consider whether patients are better off if the device is or is not available.

Preference for availability relates to both the patient and the caregiver. FDA and industry, where appropriate, should understand whether patients and caregivers would prefer to have access to the device relevant to the nonconformity or regulatory non-compliance and whether patients and caregivers adequately understand related benefits and risks.

Nature of violations/Nonconforming product may include whether the violation was systemic or non-systemic in nature as well as the extent of any product nonconformity.

Firm compliance history may include the manufacturer's regulatory history and initiative in identifying and correcting issues, the repetitiveness of such issues, and the manufacturer's

communication with FDA. When considering the firm's compliance history, FDA may determine that it is appropriate to provide prior notice to the manufacturer as to what is required, what violations appear to exist, and, in the case of violations of regulatory significance, that failure to comply may result in the initiation of enforcement action.

V. How FDA Considers Benefit-Risk in Patient Focused Medical Device Product Availability, Compliance, and Enforcement Decisions

FDA may use a benefit-risk assessment to help the Agency make informed appropriate decisions. An FDA benefit-risk assessment for medical device product availability, compliance, and enforcement decisions begins with the existence of certain events, such as a recall, variance petition, safety signal, or medical device nonconformity, that may lead FDA to take regulatory action.

FDA initiates a benefit-risk assessment by evaluating available benefit information on the applicable medical device and assessing the benefit information by considering the relevant benefit factors described in Section IV and in Appendix B – Worksheets for Benefit Assessments. Some potential sources of benefit information include literature, prior premarket submissions, clinical studies, registries, patient input, knowledgeable clinicians, and risk management documentation voluntarily supplied by the manufacturer.

FDA would next assess the available risk information on the medical device and assesses the risk information by considering the relevant risk factors described in Section IV and Appendix C – Worksheets for Risk Assessments. Some potential sources of risk information include medical device reports (MDRs), inspection reports, literature, prior premarket submissions, clinical studies, registries, patient input, knowledgeable clinicians and risk management documentation voluntarily supplied by the manufacturer.

FDA would complete the benefit-risk assessment by considering any factors from Appendix D that are relevant for assessing decision options.

When appropriate, FDA would use the outcome of a benefit-risk assessment to inform decisions related to product availability. The types of product availability decisions where this may be useful include:

- When should a firm's recall strategy appropriately include a correction instead of a removal?
- What actions, if any, may FDA take when continued access to a nonconforming device or a device manufactured by a firm with regulatory compliance issues might be needed during a shortage situation?
- When is it in the best interest of the public health to grant a variance from certain QS regulation requirements for QS issues identified during a PMA pre-approval inspection?
- When might FDA exercise enforcement discretion and not take immediate action against a company for marketing a device with a significant change or modification prior to obtaining clearance, as required by 21 CFR 807.81(a)(3)?

Before making a decision that is likely to affect product availability, FDA may also consider the impact on the patient if the device is available or not available, whether the issue affects a single manufacturer or the whole industry, and patient or caregiver preference for availability. Specific benefit-risk assessments should be viewed in the larger context that includes consideration of the additional factors described in Section IV.C, but generally, if the benefit-risk assessment indicates high benefit to patients with little risk, FDA may be more likely to decide that it is appropriate for patients to have access to a nonconforming device while the long-term corrective action is taken if alternative treatments are not available. Alternatively, if the benefit-risk assessment indicates low benefit to patients with high risk, FDA would be more likely take action to limit product availability.

In addition to compliance and enforcement decisions that potentially have a direct effect on product availability, when appropriate, FDA may use the outcome of a benefit-risk assessment to inform other decisions related to compliance and enforcement. Examples of the other types of compliance and enforcement decisions where this may be useful include:

- Is a manufacturer's proposed correction strategy adequate given the benefit-risk assessments and mitigation activities?
- Upon observing a violation, when might FDA send a Warning Letter or Untitled Letter and when would it be appropriate to take an alternative, more informal approach?

When making compliance and enforcement decisions that are unlikely to directly affect product availability, FDA may also consider whether regulatory non-compliance increases risk of harm to patients, whether taking (or not taking) a contemplated compliance or enforcement action would impact patients, the manufacturer's regulatory history, and steps taken by the manufacturer to address the situation. Specific benefit-risk analyses will again need to be viewed in context, but generally, if FDA's benefit-risk assessment indicates high benefit to patients with little risk, FDA may decide to work with the manufacturer to address the underlying issue without initiating a formal compliance or enforcement action. If FDA's benefit-risk assessment indicates low benefit to patients with high risk, FDA would likely take formal compliance or enforcement action to address the problem.

VI. Examples Demonstrating Benefit-Risk Assessments for Medical Devices

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 FDA decision. 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 draft guidance, including how we assess benefits and risks during product availability, compliance, and enforcement decisions. Similar scenarios may result in different outcomes depending on the circumstances.

A. Examples Related to Product Availability Decisions

Example 1: Recall and shortage

Background: An implantable coated device was developed which reduced thrombosis by more than 80%. There were three field complaints for a malfunction in the device's first few months of wide scale commercial use. This malfunction represented an anticipated failure mode that occurred more frequently than expected. During these events associated with the malfunction, blood loss occurred, but no serious injuries occurred. The manufacturer submitted MDRs for these events.

Removal of the product from the field would have resulted in the cancellation of hundreds of surgeries. However, the company recognized that it had product in the field with a postmarket quality nonconformity requiring a correction or removal, which must be reported to FDA under 21 CFR 806.10. The company proposed to send a communication to the field alerting users to the risk related to the nonconformity and to continue monitoring the events in the field to better understand how best to address the issue in the long term.

Benefits: The patient population for this device includes those patients at elevated risk of thrombosis. As noted above, this device reduces thrombosis by more than 80%. The likelihood of the benefit was high. A reduction in thrombosis has significant impact on patient outcomes. The magnitude of the benefit was high. There were no other comparable treatment options.

Risks: For the different patient subpopulations that may be treated with the device, FDA considered the risks of additional blood loss and increased associated surgery time should a device with this nonconformity be used. Three malfunctions with no serious adverse events had been reported. The severity of the risk was low. The manufacturer shared information indicating that 3000 devices had been implanted. The likelihood of the risk appears low.

Patient tolerance for risk and perspective on benefit: Patients appreciate the benefit of limiting thrombosis. Thrombosis is a concern for many patients and caregivers using these types of devices.

Uncertainty: FDA considered the uncertainty of the adverse event rate. It was unclear if the adverse event rate would increase. There were 300 patients in a clinical trial, and there had been 3000 devices implanted in the first few months of wide scale commercial use. As experience with the device increases, if the number of adverse events and the number of implantations are accurately tracked, the uncertainty regarding the adverse event rate would decrease.

Mitigation: FDA reviewed the manufacturer's risk management information, including how this malfunction can be addressed during surgery to minimize the impact on the patient. FDA also reviewed the proposed communication to physicians explaining the issue.

Patient impact: FDA considered the impact on patients if the device was not available in the marketplace, which included delayed surgeries or treatment with a less beneficial device.

Decision: FDA found the benefits to be high and the risks to be low in this situation. The manufacturer shared highly detailed information with FDA, which allowed FDA to better understand the malfunction rate and mitigation methods. After conducting a Health Hazard

Evaluation, FDA classified this recall as a Class II[5] recall and agreed that the proposed communication to the device users was in the best interest of public health. FDA and the manufacturer continued actively monitoring the situation to determine the most appropriate long-term solution.

Example 2: Evaluation of a variance petition

Background: A drug delivery system was developed that included a safety feature not available with other medical devices. This system is programmable to automatically suspend drug delivery when it detects that a predefined threshold has been reached. FDA noted inspectional observations for deviations from the QS regulation during a PMA pre-approval inspection of the drug delivery system manufacturer's facility. The manufacturer petitioned for a variance under section 520(f)(2) of the FD&C Act (21 U.S.C. 360j(f)(2)) and 21 CFR 820.1(e) from those sections of the QS regulation for which there were inspectional observations.

Benefits: The medical device had a safety feature to stop drug delivery not available on medical devices already on the market. The unique safety feature stopped drug delivery when the medical device detected that continued delivery of the drug was no longer indicated and could be harmful. The magnitude and likelihood of benefit is high.

Risks: Several observations of non-compliance with the QS regulation were identified during the pre-approval inspection. Specifically, the manufacturer did not have a well-functioning CAPA (corrective and preventive action) system, and several processes lacked documented procedures. The CAPA system observations did not have a direct impact on patient safety. There was no indication that nonconforming devices had been released. FDA determined that the severity and likelihood of risk related to the observations of non-compliance were low in this case, although this does not mean that non-compliance with CAPA regulations is generally low risk.

Patient tolerance for risk and perspective on benefit: Data collected during clinical trials show that patients and caregivers highly valued this unique safety feature, as it greatly decreased overdose related fears.

Mitigation: As part of the variance, the manufacturer agreed to resolve all of the QS violations by a set date, and to proactively contact all of the users of the medical device every 90 days to collect information about the medical device and any malfunctions that might have occurred. The manufacturer also agreed to investigate all complaints and provide quarterly reports detailing the results of its surveillance program related to the device to FDA.

Decision: FDA agreed that the proposed variance plan provided methods and controls that satisfied FDA's concerns in the areas where the QS violations were identified and that were sufficient to

[5] "*Recall classification* means the numerical designation, i.e., I, II, or III, assigned by the Food and Drug Administration to a particular product recall to indicate the relative degree of health hazard presented by the product being recalled." 21 CFR 7.3(m).

assure that the device will be safe and effective. Given the need in the patient community for a medical device with the unique safety feature, FDA determined that granting the variance was in the best interest of the public health.

Example 3: Continued access to nonconforming product

Background: A biological indicator used in monitoring hospital steam sterilization was not performing as expected in the field. The manufacturer initiated a voluntary recall, which it reported to FDA under 21 CFR 806.10. During its internal investigation of this postmarket quality nonconformity, the manufacturer determined that the source of the problem was with the manufacturing line and identified which lots were and were not impacted. FDA classified this recall as Class II.

The manufacturer had no history of regulatory noncompliance. It opened a CAPA item to address the root cause of the problem and notified FDA that the long-term correction would result in a decrease in the volume of biological indicators available to hospitals. The decrease in volume was projected to last for 18 months. Within a few months, FDA received notification from multiple sources that surgeries were being delayed due to the lack of biological indicators. The manufacturer provided information regarding the level of certainty for successful completion of a sterilization cycle when using the nonconforming biological indicators in accordance with proposed modified labeling. After consulting with FDA, the manufacturer determined that the proposed labeling change was one that would require submission of a new 510(k) under 21 CFR 807.81(a)(3).

Benefits: The manufacturer provided information on the benefit of using the nonconforming biological indicators according to the modified labeling. While the benefit had decreased from the anticipated benefit considered for conforming biological indicators during premarket review, the benefit for this use of the nonconforming biological indicators remained high and included an assurance of sterility and a reduction in surgical delays.

Risks: FDA considered the risks associated with use of nonconforming biological indicators. FDA received no reports of infection or injury related to the biological indicator or the hospital steam sterilizers for the time that the nonconforming biological indicator was in the field. FDA also recognized that a properly maintained and operated sterilizer is expected to result in effective sterilization cycles; the biological indicators provide confirmation. Based on the data and information available to FDA, the likelihood of risk of harm to patients was assessed to be low if the nonconforming biological indicators were used in accordance with the proposed modified labeling.

Mitigation: In this situation, there was no mitigation that could render the benefit-risk profile of the nonconforming biological indicators sufficiently positive to justify the continued use of the nonconforming device, without some additional mitigation step. The manufacturer's proposal to modify labeling for the nonconforming devices mitigated potential harm to patients.

Patient tolerance for risk and perspective on benefit: Patient perspective on risks associated with the nonconforming biological indicators was not readily available. Contact with hospitals indicated that they were seeking FDA's assistance on how best to manage the shortage of biological

indicators needed to monitor steam sterilization cycles while still protecting their patients from the potential use of non-sterile devices.

Patient impact: FDA considered the impact on patient health and quality of life if the nonconforming biological indicators were not available, which included delayed surgeries or prioritization of critical surgeries over other surgeries as a result of rationing biological indicators.

Decision: In this situation, where alternatives were not readily available, FDA worked with the manufacturer to identify data that supported use of the nonconforming biological indicators with the proposed modified labeling. FDA concluded that it would not take action against the manufacturer for marketing the nonconforming biological indicators with that labeling modification while the manufacturer worked to implement its long-term correction and while the decreased volume of conforming biological indicators continued. FDA determined that this course of action would provide the most beneficial option for patients compared to other options. Consequently, the company was able to provide the marketplace with a sufficient volume of biological indicators while correcting the underlying problem.

B. Examples Related to Compliance and Enforcement Decisions

Example 1: Evaluating whether to send a Warning Letter or take an alternative approach

Background: During an inspection of an aesthetic device manufacturer's facility, FDA investigators observed, among other things, that the firm did not maintain adequate complaint files. Noted deficiencies in the complaint system included a backlog of complaints related to the device that the manufacturer had not evaluated to determine if an MDR or investigation was necessary and pending complaint investigations that remained unresolved after more than six months without explanation. The manufacturer did not submit a response to the Form FDA 483 (FDA 483), List of Inspectional Observations issued at the close of the inspection.

Benefits: Reported clinical studies demonstrated that some patients treated saw long-term aesthetic improvement. The magnitude and likelihood of benefit for the device was assessed to be moderate. However, the device was not medically necessary, and there was no evidence that it provided a unique treatment effect or benefit compared to similar devices on the market.

Risks: The likelihood and severity of risk for similar devices was low. During the inspection, however, the FDA investigator's review of a sample of the complaints received for the device indicated that some patients had experienced adverse events of varying severity. Based on the information in those complaints, it was unclear if those adverse events may have been caused by use of the device. Without additional information, FDA could not determine the likelihood of risk for the device.

Patient tolerance for risk and perspective on benefit: There was information indicating that patients preferred similar devices on the market.

Uncertainty: The significant deficiencies in the manufacturer's complaint system created uncertainty about the risks for this device: the manufacturer could not provide complete information regarding the number of complaints involving adverse events and the failure to timely and adequately evaluate complaints may have allowed malfunctions, defects, or other nonconformities to go undetected.

Patient impact: FDA determined that there would be no substantial negative impact for patients if it issued a Warning Letter. Patients or healthcare professionals reluctant to choose a device for which a Warning Letter has been issued would have alternative products available, and there was not a strong patient preference for the device.

Firm compliance history: Some of FDA's observations related to the manufacturer's complaint handling system were repeat observations that had been noted during the previous inspection.

Decision: After thorough evaluation, FDA decided to issue a Warning Letter to the firm and to investigate further whether the device may have caused adverse events. Although the device provided a moderate benefit, that benefit was available to patients through alternatives, and there was significant uncertainty regarding the likelihood of risk for the device. In addition, the failure to correct previously noted deficiencies in its complaint system and the failure to respond to the FDA 483 indicated that less formal communications with the firm might be ineffective for achieving compliance and minimizing risk to patients. If, after gathering further information regarding adverse events, FDA determined that the device presented a higher risk to patients, the Agency would consider taking additional action, including action to limit availability of the device.

Example 2: Evaluation of potential actions following an inspection with observed Quality System deficiencies

Background: FDA's inspection of a manufacturing facility for a spinal fixation system intended for posterior, non-cervical pedicle fixation resulted in the issuance of an FDA 483, which noted, among other things, two complaint records that lacked evaluations to determine if an MDR was required to be filed, a CAPA record with no documentation of an investigation, and deficiencies in a process validation. This was FDA's first inspection of the facility, and some deficiencies were more significant than others, although none of the deficiencies were significant enough to warrant a Warning Letter. FDA conducted a benefit-risk analysis as part of its evaluation of whether to issue an Untitled Letter or to engage with the firm in a less formal manner, such as in a regulatory meeting.

Benefits: This firm's particular spinal fixation system had unique features that made it less invasive and therefore associated with a shorter surgical time than other devices of its type. Clinical studies included in the premarket submission for the device demonstrated patient benefits, including quicker recovery and reduced postsurgical pain. The magnitude and likelihood of the benefit for this device were assessed to be high.

Risks: The two complaints that lacked an evaluation for whether an MDR must be submitted did not involve a death or serious injury, and searches of FDA's Manufacturer and User Facility Device Experience (MAUDE) database revealed no MDRs reporting that the device may have caused or contributed to a death or serious injury. The likelihood of risk to patients was assessed to

be low. FDA reviewed the firm's nonconformance data during and after the inspection and determined that it was within the expected parameters for the device. There was no indication that nonconforming product had been released.

Patient tolerance for risk and perspective on benefit: FDA considered patient preference. Patients expressed a strong preference for this spinal fixation system because of the reduction in pain and recovery time.

Mitigation: The firm's responses to the FDA 483 issued at the end of the inspection indicated the firm's identification and early implementation of voluntary corrective actions that appeared to be significant steps to achieve compliance.

Nature of violations/Nonconforming product: In addition, the inspection did not reveal evidence of widespread QS deficiencies or nonconformities that were attributed to other failures in the Quality System.

Firm compliance history: This manufacturer had no history of regulatory non-compliance.

Decision: Since, among other things, the firm's nonconformance data was within the expected parameters for the device, FDA determined that there was low risk to patients associated with the inspectional observations. After careful consideration of all available information, FDA pursued a regulatory meeting with the firm instead of issuing an Untitled Letter to address the manufacturer's inspectional deficiencies. FDA decided that, in this lower risk situation, a regulatory meeting would be the most efficient means of achieving compliance, as it would engage the manufacturer in a dialogue on its proposed corrections/corrective actions. If the manufacturer fails to progress toward voluntary compliance in a timely manner, then FDA may consider conducting a follow-up inspection, issuing a Warning or Untitled Letter, or other consequences.

Appendix A - Intersection of this Draft Guidance with ISO 14971: *Medical devices – Application of risk management to medical devices*

ISO 14971 provides medical device manufacturers with a framework to systematically manage the risks to people, property and the environment associated with the use of medical devices. Specifically, the standard describes a process through which the medical device manufacturer can identify hazards associated with a medical device, estimate and evaluate the risks associated with these hazards, control these risks, and monitor the effectiveness of those controls throughout the product's life cycle. Implementing this standard requires the user to make decisions on the acceptability of individual risks, and overall residual risk for a medical device throughout its life cycle.

ISO 14971 is an FDA-recognized standard, and assuring conformity with this standard may help device manufacturers meet the requirements specified in the design controls section (21 CFR 820.30) and other sections of 21 CFR Part 820. Both ISO 14971 and 21 CFR Part 820 take a total life cycle approach to management of risks associated with medical devices, and expect that manufacturers will incorporate postmarket data into their device risk management process, including new and changes to existing risks identified after the device is on the market.

This draft guidance document provides a benefit-risk framework for FDA and stakeholders regarding use of benefit-risk information in medical device product availability, compliance, and enforcement decisions. Good documentation of risk management decisions by manufacturers may help to streamline these decisions for both FDA and manufacturers, produce outcomes for patients that deliver the most benefit for the least amount of risk, and provide a reasonable assurance of safety and effectiveness.

Appendix B - Worksheets for Benefit Assessments

The following worksheet identifies factors that may be considered in the assessment of benefit for product availability, compliance and enforcement decisions across the total product life cycle.

Anticipated benefit	Initial assessment during design and testing	Current assessment
Type of benefit(s)	What is the medical device's anticipated impact on clinical management and patient health? What benefits were initially anticipated? Was a clinical trial conducted? What benefits were expected based on similar devices?	What is the medical device's impact on clinical management and patient health? Does the marketed product achieve the anticipated benefits? Have additional benefits been observed?
Magnitude of benefit(s)	For each benefit assessed: What was the medical device's originally anticipated impact on patient health and clinical management? What was the originally anticipated effect of the device on patient management and quality of life, likelihood of survival, improving patient function, preventing loss of function, or providing relief from the symptoms of the disease or condition? What was the anticipated magnitude of each treatment effect? What scale is used to directly measure the anticipated benefit? How did the anticipated benefit rank on that scale? Is the device life supporting or life sustaining?	For each benefit assessed: What is the medical device's impact on patient health and clinical management? Is the effect of the device on patient management and quality of life, likelihood of survival, improving patient function, preventing loss of function, or providing relief from the symptoms of the disease or condition as anticipated? Did the magnitude of each treatment effect increase or decrease? For each benefit assessed, does real world data demonstrate the same rate of successful diagnosis or treatment? Has the benefit rank on that scale increased or decreased over time? Has real world practice led to new benefits?

Anticipated benefit	Initial assessment during design and testing	Current assessment
Likelihood of patients experiencing one or more benefits	What proportion of patients was expected to benefit from the device? Did the original labeling indicate which patients will experience a benefit? How did the benefits assessed vary across subpopulations? Was there a variation in public health benefit for different populations?	Using real world data or other data collection, what proportion of patients have been observed to benefit from the device? Has the likelihood of a patient within a subpopulation experiencing benefit changed? Has there been a change in variation of benefits across sub-populations? Has use of the medical device exposed a variation in public health benefit for different populations?
Duration of effects	Does the device cure a disease or provide a temporary treatment? Could the duration, if relevant, of each treatment effect, be determined? If so, what was it?	Is the duration of effect consistent with the anticipated duration of effect? Were there assumptions that proved to be inaccurate?
Patient preference on benefit	What is the severity of the disease state? Is this a chronic disease? If chronic, can the illness be managed with other treatments or therapies? How long do patients live with the disease? Even if the benefit is in a small portion of the population, do those patients who would experience the benefit value it? Is the duration of the benefit achieved of value to patients? How much do patients value this treatment? Does the treatment improve overall quality of life? Are the benefits of the medical device well understood? Is communication regarding change in benefit realistic?	What is the severity of the disease state? Is this a chronic disease? If chronic, can the illness be managed with other treatments or therapies? How long do patients live with the disease? Even if the benefit is in a small portion of the population, do those patients who would experience the benefit value it? Is the duration of the benefit achieved of value to patients? How much do patients value this treatment? Does the treatment improve overall quality of life? Are the benefits of the medical device well understood? Is communication regarding change in benefit realistic?
Benefit factors for healthcare professionals or caregivers	Were there anticipated benefits to healthcare professionals or caregivers?	Does real world experience change the understanding of benefits to professionals or caregivers?

Anticipated benefit	Initial assessment during design and testing	Current assessment
Medical necessity	Is the device essential to the survival of patients? Are alternative treatments available? What other therapies are available for this condition? How effective are the alternative treatments? How well-tolerated are the alternative therapies?	Is the device essential to the survival of patients? Are alternative treatments available? What other therapies are available for this condition? How effective are the alternative treatments? How well-tolerated are the alternative therapies? How have treatment options changed since medical device development?

Appendix C - Worksheets for Risk Assessments

The following worksheet identifies factors that may be considered in the assessment of risk for product availability, compliance and enforcement decisions across the total product life cycle.

Risk categories	Initial assessment during design and testing	Current assessment
Factors Related to Risk Severity		
Medical device-related deaths and serious injuries	What serious adverse events related to this medical device were known when FDA authorized the device for marketing? Were there any variations in serious adverse events among subpopulations?	Have medical device-related deaths or serious injuries occurred at expected severity? Are there unanticipated deaths or serious injuries? Were there any changes variations of serious adverse events among subpopulations?
Medical device-related non-serious adverse events	What non-serious adverse events related to this medical device were known at medical device clearance or approval? Were there any variations in temporary injury and medically reversible injuries among subpopulations?	Have temporary injuries related to the medical device occurred at expected severity? Have medical device-related injuries which could be medically reversed occurred at expected severity and frequency? Are there any unanticipated temporary injuries or medically reversible injuries? Were there any changes in variations in serious adverse events among subpopulations?
Medical device-related events without reported harm	What medical device malfunctions were anticipated when FDA authorized the device for marketing? Were there any variations in medical device events reported without harm among subpopulations?	Are there reports of medical device malfunctions? Are device malfunctions occurring at anticipated frequencies? Is the medical device malfunctioning in a manner that was not anticipated? Were there any changes in variations in medical device events reported without harm among subpopulations?

Duration of harm to patient	How long does the harmful event last? Is the harmful event reversible? What type of intervention is required to address the harmful event?	Is the duration of harmful events longer than anticipated? Is the harmful event still reversible? Has the type of intervention required to address the harmful event changed?
Risk factors related to Likelihood of Risk		
Likelihood of medical device nonconformity	How frequently did the manufacturer anticipate this specific failure mode or defect would occur?	How frequently does this specific failure mode or defect occur? Has the rate of medical device failures increased? Has the mean time between failures decreased? How many medical devices are expected to have a problem?
Likelihood of a harmful event given exposure to a nonconforming device		What proportion of patients treated with or diagnosed by the nonconforming medical device is harmed?
Number of patients exposed		How many patients were exposed to nonconforming devices? How many patients were exposed to a device manufactured by a noncompliant manufacturer?
Additional Risk Factors		
Nonconforming product risks		Has nonconforming product been distributed? What is the number of units on the market and market share ?
Duration of the exposure to the population		How much time elapsed between initial exposure to a risk of harm and the point at which the risk of harm is successfully addressed? How long were affected populations exposed to the nonconforming device?

Risk from false-positive or false-negative results for diagnostics	What are the consequences of a false positive? What are the consequences of a false negative? Is this the only means of diagnosing the problem, or is it part of an overall diagnostic plan?	Have the consequences of diagnostic errors changed? Have the practices related to diagnosing the problem changed? Does this increase or decrease the risk?
Patient tolerance of risk	What level of concern do patients have regarding the risks? Even if the risk is in a small portion of the population, do those patients who would experience the risk understand it? Are patients willing to take the risk of this treatment to achieve the benefit? How well are patients able to understand the risks of the treatment?	What level of concern do patients have regarding the risks? Even if the risk is in a small portion of the population, do those patients who would experience the risk understand it? Are patients willing to take the risk of this treatment to achieve the benefit? How well are patients able to understand the risks of the treatment?
Risk Factors for healthcare professionals or caregivers	Are there risks to the healthcare professional or caregiver? How significant are these risks?	Are there any changes in frequency or severity of risks for healthcare professionals and/or caregivers? Do any changes in the frequency or severity of risk for the healthcare provider or caregiver impact the risks to the patient?

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Appendix D - Worksheet for assessing potential decisions based on the Benefit-Risk Assessment Outcome

The following worksheet identifies additional factors that may be considered for product availability, compliance and enforcement decisions at all phases of the total product life cycle.

Factors	Assessment Questions
Uncertainty	What information does FDA have to assess benefit and risk? What is the quality of the information FDA is using (for example, MDRs, literature, registry or clinical trial data, limited case studies, etc.)? What is the uncertainty related to current understanding of benefits and risks?
Mitigations	Could you identify ways to mitigate the risks such as using product labeling, establishing education programs, etc.? What is the type of mitigation proposed? Is the intervention related to design, labeling, or training? Has the manufacturer corrected the cause of the nonconformity?
Detectability	Can the user easily recognize the hazard to avoid the harm? Can the problem with the medical device be corrected before use by the user?
Failure Mode	Has the manufacture identified the underlying cause? Has the firm submitted testing to the FDA? Has FDA conducted testing? What were the results?
Scope of the device issue	Are the risks identified potentially inherent to similar medical devices of this type (i.e., industry wide)?
Patient impact	What are the risks to patients if the device is not available? Are patients better off if the device is available? What are the risks to patients related to the inspectional observation or regulatory non-compliance? Does the observation or violation directly relate to product quality? Does the observed regulatory non-compliance raise concerns regarding the firm's ability to produce safe and effective medical devices?
Preference for availability	Would patients and caregivers prefer to have access to the device? Are the benefits and risks adequately understood?
Nature of violations/Nonconforming product	Was the violation systemic or non-systemic in nature? To what extent are the products nonconforming?

Firm compliance history	Has the same or a similar inspectional observation or regulatory violation been observed at the manufacturer in the past 2 years? In the past 5 years? In the past 10 years? Does the firm have a history of regulatory compliance and high quality device production? Has the firm demonstrated chronic and systematic regulatory non-compliance over time? Is the regulatory non-compliance significant enough that FDA would take regulatory action? Was the harm anticipated in the firm risk management documentation? Was the harm reported to FDA by the firm quickly? Would providing notice to the firm assist in informing the firm of its legal responsibilities?

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