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

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Guidance for Industry and Food and Drug Administration Staff

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For questions about this document regarding CDRH-regulated devices, contact the Office of Compliance at 301-796-5900.



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

Preface

Public Comment

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Guidance for Industry and Food and Drug Administration Staff

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

I. Introduction

FDA has developed this 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 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 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 guidance 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

[1] As used in this guidance, "quality" has the same meaning as in 21 CFR part 820. "*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).

this guidance—including reliable patient input[2] 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 practicable. Factors may be weighted differently for different decisions and as the timeframe allows. FDA intends to use pilots and other evaluation techniques to help determine how to apply the benefit-risk framework described in this guidance. Because of the variability in the facts of, and data available for, each decision, specific factors which will inform FDA's thinking may vary.

In addition, this guidance 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 guidance also support assessment of medical devices with real world evidence. While the benefit-risk factors in this guidance are not identical to the other frameworks, this 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 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[3]."

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 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

[2] For purposes of this guidance, "patient input" has the same meaning as set forth in FDA's Guidance for Industry, Food and Drug Administration Staff, and Other Stakeholders Patient Preference Information – Voluntary Submission, Review in Premarket Approval Applications, Humanitarian Device Exemption Applications, and *De Novo* Requests, and Inclusion in Decision Summaries and Device Labeling, August 24, 2016 ("Patient Preference Information Guidance"), http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM446680.pdf. While the Patient Preference Information Guidance focuses on FDA's consideration of patient preference information during the review of Premarket Approval (PMA) applications, HDE applications and *de novo* requests, FDA and manufacturers may use patient preference information, and other types of patient input throughout the total product lifecycle. Therefore, some recommendations in the Patient Preference Information Guidance may be helpful for manufacturers considering collection or use of patient input at other points in the product life cycle.

[3] The text version of the url for this guidance document is http://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm517504.pdf.

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 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 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 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 guidance with ISO 14971: *Medical devices – Application of risk management to medical devices* is discussed in Appendix A.

This guidance applies to both diagnostic and therapeutic medical devices subject to, and exempt from, premarket review. The scope of this 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 (EPRC) provisions in the FD&C Act and implementing regulations (21 CFR Subchapter J−Radiological Health). This 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 guidance, are not binding, and the concepts and factors described herein generally explain how benefit-risk assessments can be made. This guidance does not preclude FDA from taking regulatory or other action in response to a violation of applicable law or regulation.

III. Patient[4] 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 for patients. Considering the benefit-risk profile of the device may prevent regulatory actions with unintended adverse impact for patients (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 nonconformity in light of the benefit-risk profile of the device,[5] factoring in alternatives, where available, considering the benefit-risk balance 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 certain 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 options 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 device nonconformity, the manufacturer's 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, benefit-risk assessment worksheets have been provided to support consideration of the factors by FDA staff and industry.

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[4] Although this 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 professionals and caregivers.

[5] As used in this guidance, "nonconformity" has the same meaning as in 21 CFR part 820. "*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.)

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 input 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 guidance document may compare the benefits and risks identified based on currently available 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 evidence and data related to benefit-risk factors outlined in the 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 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 on ability to perform activities of daily living; 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. Real world evidence may show that surgeons have found 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. We encourage manufacturers wishing to provide data and calculations for use in evaluating this factor to contact FDA regarding what information may be relevant and appropriate to the issue being assessed.

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 perspective 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. Benefit factors for healthcare professionals or caregivers may include, for example, a reduction in the procedural time, improvements in overall training and utility for practitioners or caregivers with varying skill levels. 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 direct or indirect patient 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, and hazards can occur both when a device functions normally and if it malfunctions. Medical device nonconformities may 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 guidance and provides examples of how the risk factor may be considered.

Severity of harm is categorized into three levels, each of which 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[6] 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.

[6] As used in this guidance, "serious injury" has the same meaning as in 21 CFR part 803. "*Serious injury* means an injury or illness that: (1) Is life-threatening, (2) Results in permanent impairment of a body function or permanent damage to a body structure, or (3) Necessitates medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure. Permanent means irreversible impairment or damage to a body structure or function, excluding trivial impairment or damage." *See* 21 CFR 803.3(w)

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 include medical device nonconformities which have no related harm, medical device malfunctions[7] 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 or malfunction 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.

Likelihood of risk considers 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. We encourage manufacturers wishing to provide data and calculations for use in evaluating this factor to contact FDA regarding what information may be relevant and appropriate to the issue being assessed.

Distribution of nonconforming devices includes 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 level of 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

[7] As used in this guidance, "malfunction" has the same meaning as in 21 CFR part 803. "*Malfunction* means the failure of a device to meet its performance specifications or otherwise perform as intended. Performance specifications include all claims made in the labeling for the device. The intended performance of a device refers to the intended use for which the device is labeled or marketed, as defined in [21 CFR 801.4]." 21 CFR 803.3(k).

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. 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.

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. Issues that may inform the degree of uncertainty include, but are not limited to, the type of clinical information available (e.g., clinical trial data, real world evidence derived from registries or commercial experience), the degree to which the available information is representative (sample size, generalizability of the sample to the population exposed to the device), and the statistical inferences and limitations that can be drawn from the information.

Mitigations are actions taken by the manufacturer, by FDA, or by other stakeholders to recover benefit 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. Risk acceptability is assessed after any appropriate mitigation.

Detectability refers to whether 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 implant may cause a delay in surgery).

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. For example, an intermittent electrical connection due to faulty soldering (manufacturing failure) may indicate a different cause of the nonconformance than an error in wiring design that affects all devices (design failure).

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.[8]

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

An FDA benefit-risk assessment for medical device product availability, compliance, and enforcement decisions may be prompted by events—such as a recall, variance petition, new safety information or analysis, or medical device nonconformity—that may lead FDA to take regulatory action. For example, consistent with the benefit risk framework described in this guidance, FDA intends to evaluate benefit and the degree to which product remains unused in the market during health risk assessments (HRAs) that help FDA and manufacturers determine if any actions, such as recall or notifying the public regarding a risk, are necessary.

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 for the subject device (including information regarding similar competitor devices, if available), clinical

[8] For additional FDA information regarding prior notice, see Regulatory Procedures Manual Chapter 10 – Other Procedures, Section 2 – Prior Notice, updated 6/19/2015, http://www.fda.gov/ICECI/ComplianceManuals/RegulatoryProceduresManual/ucm179537.htm.

studies, registries, patient input, experienced clinicians, and risk management documentation voluntarily supplied by the manufacturer. FDA encourages manufacturers that wish to provide such documentation to do so through the designated FDA point of contact for the issue being assessed, such as by contacting a district recall coordinator in the context of a potential recall situation.

FDA would next assess the available risk information on the medical device 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 for the subject device (including information regarding similar competitor devices, if available), clinical studies, registries, patient input, experienced 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:

- 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 appropriate alternative treatments are not available. Alternatively, if the benefit-risk assessment indicates low benefit to patients with high risk, FDA would be more likely to 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 initiate advisory, administrative or judicial action, and when would it be appropriate to take a 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 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 potential shortage of a high benefit implantable coated device with low additional risk[9]

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 appeared to be occurring 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 determined that it had product in the field with a nonconformity requiring a correction or removal, which must be reported to FDA under 21 CFR 806.10. The

[9] When "additional risk" is mentioned in this guidance, it refers to the additional risk presented by a nonconformity or noncompliance.

company proposed to send to customers a communication that included a supplement to the original labeling and alerted users to the potential increased risk. The company further proposed 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. There was no indication that the malfunction affected the device's reduction 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 additional risk appeared to be 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 using these types of devices. A representative sample of patients was informed about the increased incidence of temporary and medically reversible adverse events and indicated that they generally still would prefer to use the beneficial device.

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: During the HRA, 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 users explaining the issue and the proposed supplement to the labeling.

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 additional 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 evaluating benefit and risk, the manufacturer developed a recall strategy, which included a correction through the communication that included a supplement to the labeling but did not recommend removal of the product. After

conducting a Health Hazard Evaluation, FDA classified this recall as a Class II[10] recall and agreed that the proposed correction 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 related to a high benefit drug delivery system for which risks posed by QS issues were sufficiently mitigated

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. For the currently marketed devices manufactured at the facility, 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 if corrected within a certain time period, 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 the device's unique safety feature, as it greatly decreased overdose related fears. Patients were informed that there was a small increase in risk that they may be exposed to a nonconforming device and believed that the benefits of using the drug delivery system outweighed the risks.

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.

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[10] "*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).

Decision: FDA found the benefits to be high and the risks to be sufficiently mitigated in this situation. 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 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 biological indicator with high benefit and mitigated additional risk

Background: A biological indicator used in monitoring hospital steam sterilization was not performing as expected in the field. 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. The manufacturer initiated a voluntary recall, which it reported to FDA under 21 CFR 806.10. 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 the benefit-risk profile of the nonconforming biological indicators was not 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 adequately mitigated potential harm to patients.

Patient tolerance for risk and perspective on benefit: Patient input on risks associated with the nonconforming biological indicators was not readily available.

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. 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. The hospitals expressed concern about a shortage. FDA considered this as well as other evidence and concurred with the concern.

Decision: FDA found the benefits to be high and that the proposed modification to the labeling would sufficiently mitigate risk under these circumstances. 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.

Example 4: Malfunction of a pregnancy test with low benefit and moderate additional risk

Background: A device indicated for over-the-counter (OTC) use for the detection of human chorionic gonadotropin (hCG) in urine to aid in early detection of pregnancy was determined to have a higher rate of false positive results than expected based on performance data submitted in the 510(k) for the device. A malfunction was identified after healthcare providers noticed an increase in patients reporting positive test results when using this particular device, who were not then confirmed pregnant by serum beta hCG testing. The manufacturer determined that only specific lots were affected. Lay users would be unlikely to detect the malfunction.

There are many similar pregnancy testing devices on the market, and FDA has no information suggesting that those similar devices are not performing as expected. The firm contacted FDA to discuss whether devices from the affected lots should continue to be available to patients. The firm also provided its risk management documentation assessing the benefit-risk balance for this situation.

Benefits: The device helps the patient determine whether she is pregnant. However, there are also many alternative devices on the market that are readily available to patients. Because of the potential lack of accuracy, the benefit of the devices in the affected lots is reduced.

Risks: Women with false positive results may seek unnecessary prenatal care. In addition, some OTC urine pregnancy tests are used in the health care provider setting (e.g., CLIA waived doctor's offices, outpatient centers) to rule out pregnancy so that patients can begin treatment with certain drugs, or have certain procedures. False positive results could delay these treatments, some of which may be medically necessary.

Patient tolerance for risk and perspective on benefit: Patients appreciate the benefit of an OTC test to help them determine whether they are pregnant. FDA does not have data related to patient tolerance of risk for these devices.

Mitigation: The firm did not identify a mitigation to address the additional risk related to the malfunction other than removing the affected lots from the market.

Patient impact: FDA considered the impact on patients if the device was not available in the marketplace and determined that other similar devices could provide similar benefit without the additional risk related to the malfunction.

Decision: FDA found the benefits to patients for the device with the malfunction to be low. For tests used in the health care provider setting, FDA found the risk to be moderate based on potential delay of medically necessary treatments for some patients. After conducting independent HRAs, FDA and the manufacturer both concluded that there was no need to support continued availability for the affected lots. The firm notified retailers and distributors to remove the affected lots. The manufacturer appropriately reported this action to FDA per 21 CFR 806.10. FDA classified this recall as a Class II recall and agreed that the proposed communication to the retailers and distributors to discard the affected lots was in the best interest of public health. FDA and the manufacturer continued to actively monitor the situation to determine if additional action was needed.

Example 5: Recall of a radiation therapy device with high benefit and increased risk for some patients

Background: Real world evidence and other data suggest that a radiation therapy device is less accurate than was estimated in premarket testing. In addition, real world evidence and other data have indicated that the probability of damaging healthy tissue with the device may be higher than other treatment options for some patients. The higher risk patients appear to be in an identifiable subgroup of the original population covered by the indications for use. The manufacturer assesses the issue and determines that the lower accuracy is inherent to the technology and not a result of issues with the particular device design or manufacturing process.

Benefit: Both premarket data and real world evidence indicate that the device is 80% more effective at treating certain types of aggressive cancers than other technologies on the market, and the magnitude of benefit for patients with those types of aggressive cancers is high. While other treatment options for patients with these types of cancers are available on the market, none is as effective as the radiation therapy device at issue.

Risks: The manufacturer performs a risk assessment and determines the level of risk is higher than anticipated for some patients due to the increased probability of damaging healthy tissue. Because

the higher risk patients appear to be in an identifiable subgroup of the original population covered by the indications for use, the risk for patients outside of that subgroup does not appear to have increased.

Mitigation: The manufacturer proposes updating its labeling with respect to accuracy of the device and to include a warning regarding the increased risk of healthy tissue damage for the identifiable subgroup. In addition, the manufacturer proposes issuing a customer notification letter that includes the updated labeling for devices in the field and explains that the risk may be greater than originally defined for an identifiable subgroup of the original population covered by the indications for use.

Patient impact: As noted above, the device is 80% more effective at treating certain types of aggressive cancers than other technologies on the market, thereby providing patients an option they did not otherwise have. Removing the device from the market would eliminate the device as a treatment option for patients, including those who do not appear to be at higher risk of healthy tissue damage based on the available data. If the device remains available, patients in the higher risk subgroup could be exposed to a higher risk of damage to otherwise healthy tissues if they receive treatment with the device.

Decision: FDA found the benefits of the device to be high in this situation, given its more effective treatment of aggressive cancers compared to other available technology. Although the risk of damage to healthy tissue appears to be higher than expected in a subgroup of patients, the additional warning that the manufacturer proposes to add to the labeling will help identify patients who may be affected by this risk. After reviewing the available data and the information provided by the manufacturer, FDA determines that the warning is important to the safe use of the device. FDA concurs with the manufacturer's proposed recall action, which includes a correction to make labeling changes that the firm reports to FDA under 21 CFR 806.10. Many patients who could benefit from use of the device fall outside the higher risk subgroup, and the correction would not prevent access to the device for those patients.

B. Examples Related to Compliance and Enforcement Decisions

Example 1: Evaluating whether to send a Warning Letter or take an alternative approach for a low benefit, low additional risk aesthetic device

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 were not resolved in a timely manner according to proper complaint handling processes. 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: Available information indicated that the likelihood and severity of risk for similar devices was low. During the inspection, however, the FDA investigators' review of a sample of the complaints received for the device at issue 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 considering the relevant benefit factors in aggregate, FDA found the benefit to patients to be low and the potential additional risk to be low; however, FDA did not have a high degree of certainty in the level of risk for the device. 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 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 other forms of 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 QS deficiencies regarding a high benefit spinal fixation system

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 data during and after the inspection and determined that the data were within the expected specifications for the device. There was no indication that nonconforming product had been released.

Patient tolerance for risk and perspective on benefit: FDA considered patient input. 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 QS failures.

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

Decision: FDA found the benefit to patients to be high and the potential additional risk from the QS deficiencies to be low. Since, among other things, the firm's data were within the expected specifications for the device, FDA determined that there was low risk to patients associated with the inspectional observations. After careful consideration of all available information, including real world evidence, 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 and help mitigate potential additional risk from the QS deficiencies. 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 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. There may be benefits to manufacturers in incorporating ISO 14971 into their quality management system. The concepts within ISO 14971 and output from a firm's quality management system that incorporates ISO 14971 may be used as inputs to benefit-risk assessments described in this guidance document.

This 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. This guidance document's focus is supporting these types of decisions, and the risk management language used in this guidance document is not completely harmonized with ISO 14971. Good documentation of risk management decisions by manufacturers using an ISO 14971 based risk management process may help to streamline medical device product availability, compliance, and enforcement 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. This worksheet is intended to support consideration of the factors by FDA staff and industry; its use is optional.

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?	Using real world data or other available data, 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, do 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 available data, 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 perspective 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 healthcare 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? For appropriate treatment, is it critical that the device be used without interruption? 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?

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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. This worksheet is intended to support consideration of the factors by FDA staff and industry; its use is optional.

Risk categories	Initial assessment during design and testing	Current assessment
Factors Related to Severity of Harm		
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?	Do real world data or other available data show that medical device-related deaths or serious injuries have occurred at expected severity? Are there unanticipated deaths or serious injuries? Were there any changes or 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? How long does the harmful event last? Is the harmful event reversible? What type of intervention is needed to address the harmful event?	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? Is the duration of harmful events longer than anticipated? Is the harmful event still reversible? Has the type of intervention needed to address the harmful event changed?

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?
Additional Risk Factors		
Likelihood of Risk	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? What proportion of patients treated with or diagnosed by the nonconforming medical device is harmed? How many patients were exposed to nonconforming devices? How many patients were exposed to a device manufactured by a noncompliant manufacturer?
Distribution of Nonconforming Devices		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?

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. This worksheet is intended to support consideration of the factors by FDA staff and industry; its use is optional.

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, inspectional data etc.)? Is the quality of information a reliable source for making an objective and unbiased benefit or risk decision? 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 is the potential impact on 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?