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Draft Guidance: Factors to Consider regarding Benefit-Risk in Medical Device Product Availability, Compliance and Enforcement Decisions

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

Draft Guidance for Industry and Food and Drug Administration Staff

DRAFT GUIDANCE

This draft guidance document is being distributed for comment purposes only.

Document issued on June 16, 2016.

You should submit comments and suggestions regarding this draft document within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to <http://www.regulations.gov>. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Identify all comments with the docket number listed in the notice of availability that publishes in the *Federal Register*.

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

Key Points from the Draft Guidance

- Complements the premarket Benefit-Risk Guidance documents
- Shared Benefit-Risk Framework
- Includes Product Availability and Compliance and Enforcement Decisions
- Balances FDA authority vs. Patient Benefit
- Describes of Benefit-Risk Factors
- Provides Examples and Worksheets



Excerpts from the Draft Guidance

NOTE: The following slides contain parts of the Draft Guidance “Factors to Consider Regarding Benefit-Risk in Medical Device Product Availability, Compliance and Enforcement Decisions.”

This Draft Guidance is **available for comment** and text *may* change!

Excerpts—I. Introduction

“FDA has developed this draft guidance document to **provide clarity** for FDA staff and industry regarding the benefit and risk factors the FDA may consider in prioritizing resources for **compliance and enforcement** efforts to maximize medical device quality and patient safety...

The FDA believes that explaining how we consider the factors listed in this draft guidance document will **improve** the consistency and transparency of these kinds of decisions.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.” (See pp.4)

Excerpts—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).”

Excerpts—II. Scope

For example, the FDA may consider the benefit-risk factors during:

- 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.”

II. Scope

The factors described in this document can apply to:

- product availability
- compliance and enforcement decision making

Excerpts—III. Patient Focused Benefit-Risk Assessments

- The FDA has the authority to limit the availability of violative medical devices.
- Decisions should be made while focusing on the impact on patients.
- Failure to consider the impact of non-compliance may result in regulatory actions with unintended adverse effects for patients.
- The FDA and industry can help maximize benefits and reduce risks to patients by:
 - Assessing the situation
 - Considering patients’ perspectives
 - Evaluating regulatory non-compliances
 - Factoring in alternatives
 - Considering benefit-risk tradeoffs
 - Determining the most appropriate next steps

Assessing Medical Device Risks

- Risk Severity
- Nonconforming product risks
- Duration of exposure to population
- False positive or false negative results
- Patience tolerance of risk
- Risk factors for health care professionals or caregivers

IV. Factors to Consider Regarding Benefit-Risk

- Factors for the Assessment of Medical Device Benefits
- Factors for the Assessment of Medical Device Risks
- Factors to Consider When Making Product Availability, Compliance, and Enforcement Decisions Based on the Benefit-Risk Evaluation Outcome

Assessing Medical Device Benefits

- Type of Benefit
- Magnitude of benefit(s)
- Likelihood of patients experiencing one or more benefits
- Duration of effects
- Patient preference on benefit
- Benefit factors for health care professionals or caregivers
- Medical necessity

Additional Benefit-Risk Factors to Consider

- Uncertainty
- Mitigations
- Detectability
- Failure mode
- Scope of the device issue
- Patient impact
- Preference for availability
- Nature of violations/Nonconforming product
- Firm compliance history

V. How FDA Considers Benefit-Risk

- FDA identifies an issue
- Gathers available benefit information
- Gathers available risk information
- Considers relevant additional factors

Excerpts—V. How the FDA Considers Benefit-Risk

“The types of product availability decisions where this may be useful include:

- Correction vs. removal on behalf of the firm
- FDA actions to keep products available in the market during shortage situations
- When to grant a variance from certain QS regulation requirements for QS issues identified during a PMA pre-approval inspection
- When to 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)” (See pp. 14)

Excerpts—V. How FDA Considers Benefit-Risk

“The types of compliance and enforcement decisions where this may be useful include:

- Determining the adequacy of manufacturer’s proposed correction strategy in light of the benefit-risk assessments and mitigation activity
- Determining the adequacy of manufacturer’s proposed correction strategy in light of the benefit-risk assessments and mitigation activity (See pp.14)

Excerpts—V. How FDA Considers Benefit-Risk

“Specific benefit-risk analyses will again need to be viewed in context, but generally,

- If the 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 an enforcement action.
- If the benefit-risk assessment indicates low benefit to patients with high risk, FDA would likely take compliance or enforcement action to address the problem.” (See pp.14)

VI. Examples Demonstrating Benefit-Risk Assessments

Examples Related to Product Availability Decisions

1. Recall and shortage
2. Evaluation of a variance petition
3. Continued Access to Nonconforming Product

Examples Related to Compliance and Enforcement Decisions

1. Evaluation of whether to send a Warning Letter or take an alternative approach
2. Evaluation of potential actions following an inspection of a manufacturer with observed Quality System deficiencies

Appendix A—Intersection of this Guidance with ISO 14971

EUROPEAN STANDARD

EN ISO 14971

NORME EUROPÉENNE

EUROPÄISCHE NORM

July 2012

ICS 11.340.01

Supersedes EN ISO 14971:2009

English version

**Medical devices - Application of risk management to medical
devices (ISO 14971:2007, Corrected version 2007-10-01)**

Dispositifs médicaux - Application de la gestion des risques
aux dispositifs médicaux (ISO 14971:2007, Version
corrigée de 2007-10-01)

Medizinprodukte - Anwendung des Risikomanagements auf
Medizinprodukte (ISO 14971:2007, korrigierte Fassung
2007-10-01)



Appendix B - Worksheets for Benefit Assessments

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?



Appendix B - Worksheets for Benefit Assessments

Anticipated benefit	Initial assessment during design and testing	Current assessment
<p>Magnitude of benefit(s)</p>	<p>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?</p>	<p>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?</p>

Appendix C - Worksheets for Risk Assessments

Risk categories	Initial assessment during design and testing	Current assessment
<u>Factors Related to Risk Severity</u>		
Medical device-related deaths and serious injuries	<p>What serious adverse events related to this medical device were known at clearance or approval?</p> <p>Were there any variations in serious adverse events among subpopulations?</p>	<p>Have medical device-related deaths or serious injuries occurred at expected severity? Are there unanticipated deaths or serious injuries?</p> <p>Were there any changes variations of serious adverse events among subpopulations?</p>

Appendix C - Worksheets for Risk Assessments

Factors Related to Risk Severity

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?



Appendix D - Worksheet Using the Benefit-Risk Evaluation Outcome

Additional factors for assessing potential decisions

Factors	Assessment Questions
Uncertainty	<p>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?</p>
Mitigations	<p>Could you identify ways to mitigate the risks such as using product labelling, establishing education programs, etc.? What is the type of mitigation proposed? Is the intervention related to design, labelling, or training? Has the manufacturer corrected the cause of the nonconformity?</p>

Appendix D - Worksheet Using the Benefit-Risk Evaluation Outcome

Additional factors for making Product Availability decisions

Factors	Assessment Questions
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?
Preference for availability	Would patients and caregivers prefer to have access to the device? Are the benefits and risks adequately understood?

Appendix D - Worksheet Using the Benefit-Risk Evaluation Outcome

Additional factors for making other Compliance and Enforcement Decisions

Factors	Assessment Questions
Patient impact	<p>What are the risks to patients related to the inspectional observation or regulatory non-compliance?</p> <p>Does the observation or violation directly relate to product quality?</p> <p>Does the observed regulatory non-compliance raise concerns regarding the firm's ability to produce safe and effective medical devices?</p>
Nature of violations/Non-conforming product	<p>Was the violation systemic or non-systemic in nature?</p> <p>To what extent are the products nonconforming?</p>



Appendix D - Worksheet Using the Benefit-Risk Evaluation Outcome

Additional factors for making other Compliance and Enforcement Decisions

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 firm risk management file?

Was the harm reported to FDA by firm quickly?

Is it critical that FDA provide prior notice at this point?

To Comment on the Draft Guidance

- Docket number - FDA-2016-D-1495
- Comments due September 14, 2016
- <https://federalregister.gov/a/2016-14200>



Questions?

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will be available at:**

<http://www.fda.gov/training/cdrhlearn>

Under Heading: Postmarket Activities