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

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Objective

The objective is to understand the following:

WHAT

- Purpose and policy in the final guidance

WHEN

- When a benefit-risk assessment is recommended in a 510(k)

HOW

- How the guidance can be applied to help guide benefit-risk assessment in a 510(k)
- Factors to consider when conducting a benefit-risk assessment in a 510(k)

WHO

- Who performs a benefit-risk assessment

Background



Guidance History

- **Draft Guidance issued on July 15, 2014**
- **Nine groups/individuals submitted 96 comments**
 - Medical device manufacturers
 - Trade organizations
 - Patient and consumer advocacy groups
 - Public citizens
- **Revisions to the draft guidance fell into one of the three (3) categories:**

Clarified that the guidance does not change the current 510(k) process or SE standard

Clarified that benefit-risk assessment does not imply submission of clinical data

Clarified what is expected in a 510(k) benefit-risk assessment



How To Use A Guidance Document

Guidance is **not binding on FDA or the public**

Draft guidance

Intended for input and not for implementation

Final guidance

Represent the current thinking of the FDA on a particular topic.

Alternative approach from policy outlined in a guidance document should be documented with appropriate justification and supervisory concurrence.

Final Guidance Overview

Scope

- This guidance outlines the policy for evaluating substantial equivalence in a 510(k) when the benefit-risk profile of a new device is different from that of the predicate device based on performance data.

Situations When Benefit-Risk Assessment is Recommended

- An increase in risk and increase or equivalent benefit (↑/↑=) or
- A decrease in benefit and a decrease or equivalent risk (↓/↓=) when comparing a new device to a predicate device.

Performance Data in 510(k)

- Valid scientific evidence is used to establish the probable benefits and risks of a device compared to a predicate device. Valid scientific evidence can include both non-clinical and/or clinical performance data.

Benefit Risk (B-R) Factors to Consider

- Guidance outlines factors to consider when comparing the benefit-risk profile of a new device and a predicate device to determine substantial equivalence such as magnitude of benefit, severity of risk, probability and uncertainty.

Example Section

- Guidance includes examples scenarios which walk through whether a benefit-risk assessment is recommended, and if so, factors for consideration and how the benefit-risk assessment informed the SE determination.

Implementation of 510(k) Benefit Risk Guidance

This guidance **does not** change the 510(k) premarket review standard or create extra burden on a submitter to provide additional performance data from what has traditionally been expected for 510(k)s.

510(k) Benefit-Risk Guidance:

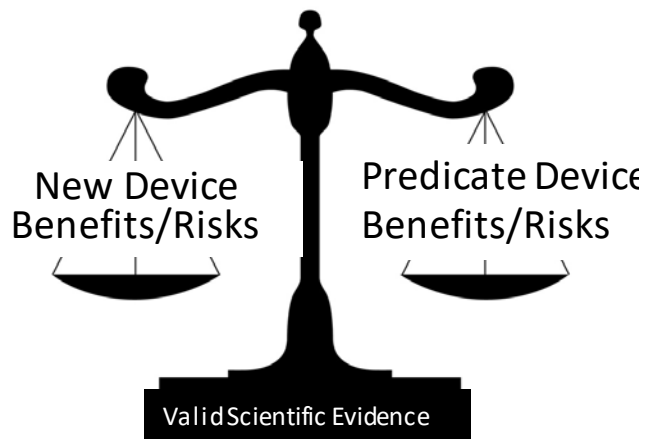
- Serves as **an aid** for evaluating benefit-risk factors to determine substantial equivalence (SE) in a 510(k)
- Provide guidance **specifically in situations when the benefit-risk profile of a new device is different from that of the predicate device**
- Provides **additional clarification** on factors that FDA takes into consideration when evaluating the benefit-risk profile of a new device when compared to a predicate device
- Improves the **predictability, consistency, and transparency** of the 510(k) premarket review process

Benefit Risk Assessment in a 510(k)

The benefit-risk framework for a 510(k) is fundamentally different from the benefit-risk (B-R) framework for other premarket submissions because a comparison is made between the benefit-risk profile of the new and predicate device in order to determine substantial equivalence.

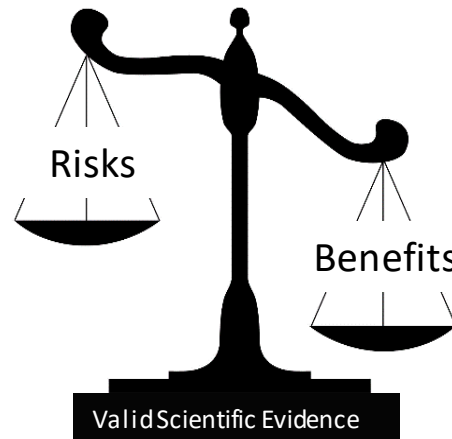
510(k) B-R Assessment

Comparison of B-R profile



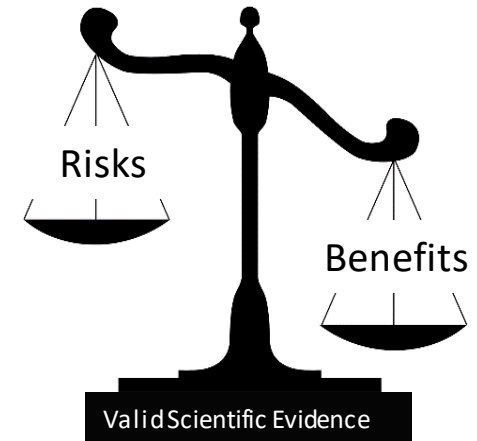
PMA/De Novo B-R Assessment

Independent assessment



IDE B-R Assessment

Independent & Investigational

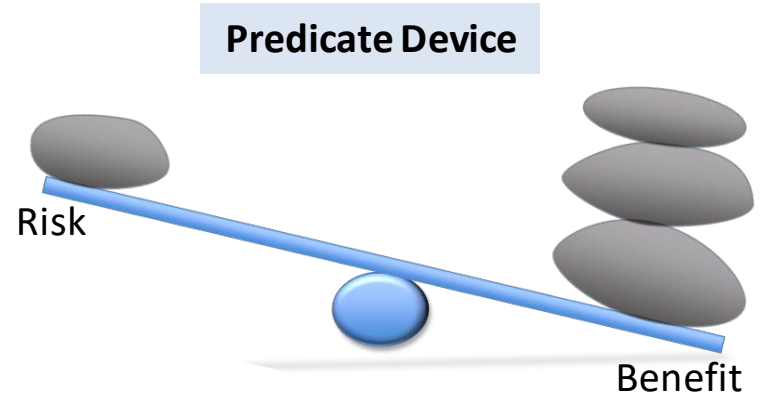
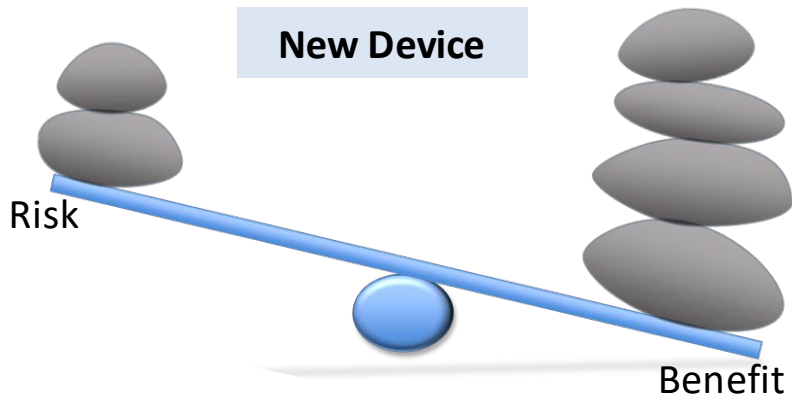


Valid scientific evidence (VSE) is used to establish the probable benefits and risks of a device. VSE can include both non-clinical and/or clinical performance data. These types of performance data are evaluated by FDA during premarket review.

NOTE: Clinical data is not common in 510(k)s.

Policy - Benefit Risk Profile Comparison

FDA understands that there might be variability in the benefit-risk profile comparison.



- Differences in benefit-risk profiles does not automatically result in a Not Substantially Equivalent (NSE) decision.
- FDA determines whether the differences impacts SE.
- Guidance is intended to provide direction when the benefit-risk profile of a new device is different from that of the predicate device.
- Guidance specifies two situations when a benefit-risk assessment is appropriate. See quadrants 1 and 3 in the table.

	INCREASE IN RISK	DECREASE /EQUIVALENT RISK
INCREASE/ EQUIVALENT BENEFIT	<p style="text-align: center; border: 1px solid #007bff; border-radius: 10px; padding: 5px; color: white;">Conducting a benefit-risk assessment is recommended.</p> <p style="text-align: right;">1</p>	<p style="text-align: center;"><u>Completing 510(k) benefit-risk worksheet is not recommended.</u></p> <p>FDA will generally determine the new device SE to the predicate device when there is increase/equivalent benefit and decreased/equivalent risk.</p> <p style="text-align: right;">2</p>
DECREASE IN BENEFIT	<p style="text-align: center;"><u>Completing 510(k) benefit-risk worksheet is not recommended.</u></p> <p>FDA will generally determine the new device NSE to the predicate device when there is a decrease in benefit and an increase in risk.</p> <p style="text-align: right;">4</p>	<p style="text-align: center; border: 1px solid #007bff; border-radius: 10px; padding: 5px; color: white;">Conducting a benefit-risk assessment is recommended.</p> <p style="text-align: right;">3</p>

Policy



Table serves as a guide for when benefit-risk assessment is recommended in a 510(k). This table should be used with the guiding principles provided in the rest of the guidance.

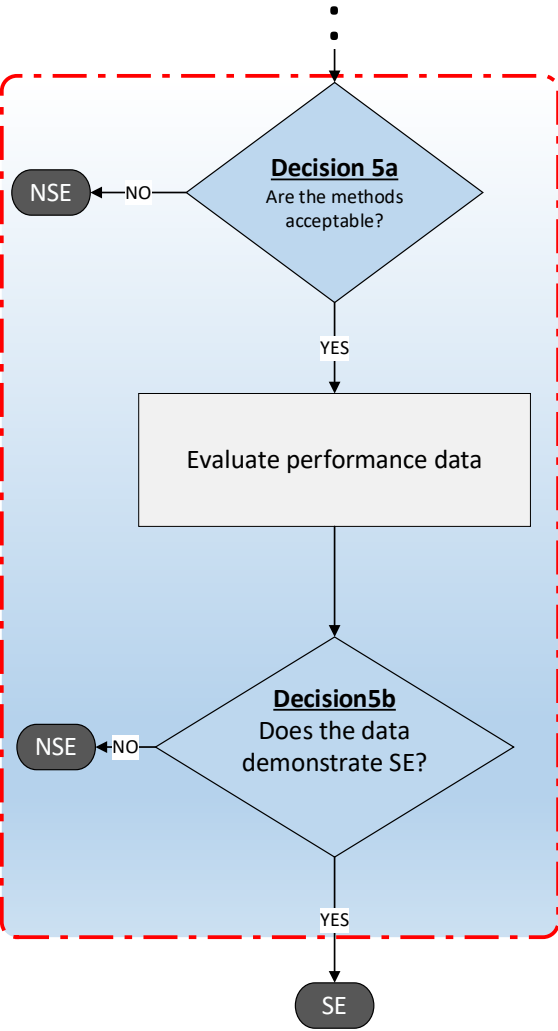
	INCREASE IN RISK	DECREASE /EQUIVALENT RISK
INCREASE/ EQUIVALENT BENEFIT	<p>Conducting a benefit-risk assessment is recommended.</p> <p>FDA evaluates the nature of the increased risk and considers whether additional measures may help to mitigate the increased risk. FDA will generally not deem a new device SE to a predicate when the increased risk cannot be mitigated and is not accompanied by an increase in benefit. 1</p>	<p>Conducting a benefit-risk assessment is likely not recommended to determine whether the new device is “as safe and effective” as the predicate device.</p> <p>FDA will generally determine the new device SE to the predicate device when there is increase/equivalent benefit and decreased/equivalent risk. 2</p>
DECREASE IN BENEFIT	<p>Conducting a benefit-risk assessment is likely not recommended to determine whether the new device is “as safe and effective” as the predicate device.</p> <p>FDA will generally determine the new device NSE to the predicate device when there is a decrease in benefit and an increase in risk. 4</p>	<p>Conducting a benefit-risk assessment is recommended.</p> <p>If the aggregate benefit of a new device is decreased in and the risk level is decreased, FDA may determine the new device to be SE if the differences do not impact whether the new device is at least “as safe and effective”. However, if there is a decrease in benefit without a decrease in risk, FDA would likely find a device NSE to the predicate especially if the benefit-risk assessment confirms that the new device is not “as safe and effective” as the predicate device. 3</p>

When during a 510(k) review can benefit-risk assessment be conducted?

After it is determined...

- That the predicate device is legally marketed
- The intended use of the new and predicate device are the same.
- Differences in technological characteristics do not raise different questions of safety and effectiveness.

[Cross reference SE guidance* containing the decision making flowchart.]



This guidance document is applicable **when a new device has the same intended use as the predicate device, and different technological characteristics do not raise different questions of safety and effectiveness.** As discussed in Sections III and IV, FDA believes this document would be most helpful in situations when there is 1) an increase in risk and increase or equivalent benefit or 2) a decrease in benefit and a decrease or equivalent risk when comparing a new device to a predicate device.

See Figure 1 in 510(k) Benefit-Risk Guidance

*[The 510\(k\) Program: Evaluating Substantial Equivalence in Premarket Notifications \[510\(k\)\]](#)

Factors to Consider When Assessing Benefit Risk

FDA evaluates the aggregate benefits and aggregate risks of a new device and compares it to that of a predicate device.

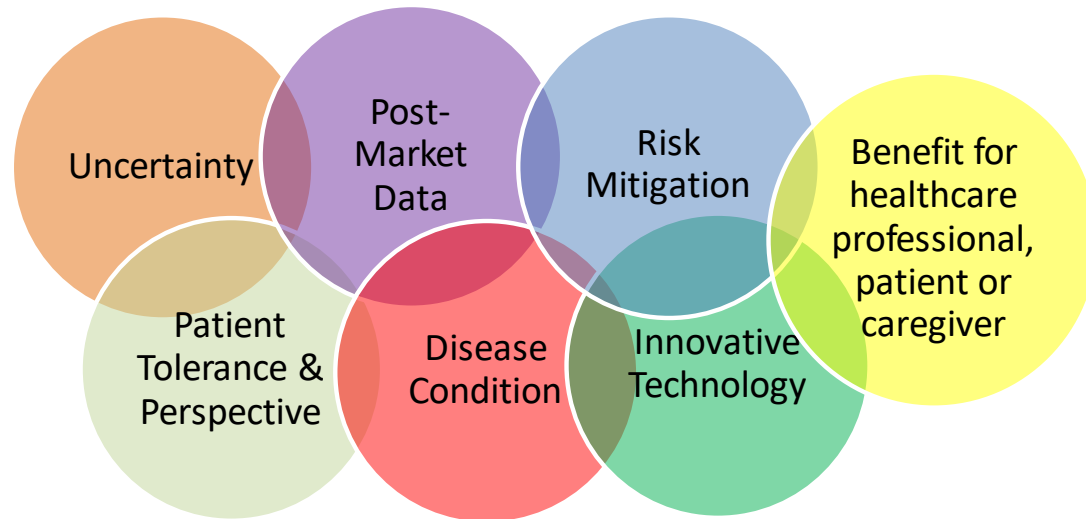
BENEFIT

- FDA considers the following factors when assessing the extent of the probable benefit(s):
 - Type of benefit(s)
 - Magnitude
 - Probability that the patient will experience one or more benefit(s)
 - Duration of effect(s)

RISK

- FDA considers the following factors when assessing the extent of probable risk(s):
 - Type of risk
 - Severity
 - Rate
 - Probability of harmful event
 - Probability that the patient will experience one or more harmful events
 - Duration of harmful event(s)
 - Risk from false-positive or false negative results for diagnostic devices

Additional Factors to Consider When Assessing Benefit-Risk



- **Uncertainty.** FDA considers the extent of uncertainty of a benefit or risk. Uncertainty may arise from quality of valid scientific evidence. (Example: Less than optimal bench testing, inadequate data analysis, poor study design, etc.)
- **Disease Condition.** Consideration of the clinical manifestation of disease/condition, how it's treated and how it affects the patient.
- **Innovative Technology.** Consideration for whether a new device has technological improvements that are important for public health.
- **Patient Tolerance for Risk & Perspective.** Consideration of how the patient tolerates risk and perceives benefit. Risk tolerance varies amongst patients.
- **Benefit for the Health Care Professional, Patient or Caregiver.** FDA recognizes that there are tools that positively affect patient management.
- **Risk Mitigation.** Use of mitigation strategies could minimize probability of a harmful event. (Example: Labeling)
- **Post-Market Data.** Post-market data could provide understanding of benefits and risks of similar device types.

Who Performs a Benefit Risk Assessment?

☐ Submitter:

- If the benefit-risk profile comparison falls in quadrants 1 or 3, the submitter can include a benefit-risk assessment in a 510(k) submission, but it is not required.

☐ FDA:

- If the benefit-risk profile comparison falls in quadrants 1 or 3, the Lead Reviewer performs a benefit risk assessment.
- If there is not sufficient information in the submission, the Lead Reviewer can request summary benefit-risk information from the submitter to help complete the benefit-risk assessment.

	INCREASE IN RISK	DECREASE /EQUIVALENT RISK
INCREASE/ EQUIVALENT BENEFIT	<div style="border: 1px solid #6c757d; border-radius: 10px; background-color: #4a7c9c; color: white; padding: 5px; text-align: center; margin: 10px auto; width: 80%;"> Conducting a benefit-risk assessment is recommended. </div> <p style="text-align: right; margin-top: 10px;">1</p>	<p><u>Completing 510(k) benefit-risk worksheet is not recommended.</u></p> <p>FDA will generally determine the new device SE to the predicate device when there is increase/equivalent benefit and decreased/equivalent risk.</p> <p style="text-align: right;">2</p>
DECREASE IN BENEFIT	<p><u>Completing 510(k) benefit-risk worksheet is not recommended.</u></p> <p>FDA will generally determine the new device NSE to the predicate device when there is a decrease in benefit and an increase in risk.</p> <p style="text-align: right;">4</p>	<div style="border: 1px solid #6c757d; border-radius: 10px; background-color: #4a7c9c; color: white; padding: 5px; text-align: center; margin: 10px auto; width: 80%;"> Conducting a benefit-risk assessment is recommended. </div> <p style="text-align: right; margin-top: 10px;">3</p>

Example Deficiency

If there is not sufficient information in the submission to complete the benefit-risk assessment, the Lead Reviewer can request for additional information.

Based on the information provided in your submission, it is not clear how the differences in benefits and risks of your device, when compared to the predicate device, impact substantial equivalence (SE). Thus, to help us understand the benefit-risk profile of your device in comparison to the predicate device, please provide the following:

- a. The **benefits** of your device (type of benefit, magnitude, probability of the patient experiencing one or more benefit, duration of effect(s))
- b. The **risks** associated with use of your device (type of risk, severity, rate, probability, duration)
- c. **Summary of any additional factors** to be taken into consideration (e.g., uncertainty, risk mitigation, post-market data, innovative technology, patient perspective)
- d. **Conclusion** on whether the benefits associated with use of your device outweighs the risks in comparison to the predicate device

This information will help us conduct a benefit-risk assessment and inform our substantial equivalence (SE) decision. In your response, we recommend that you consider the factors outlined in the guidance “Benefit-Risk Factors to Consider When Determining Substantial Equivalence in Premarket Notifications (510(k)) with Different Technological Characteristics”

<https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM404773>).

Please note that a summary of how the benefit-risk assessment was used to support SE should be included in your 510(k) Summary consistent with 21CFR 807.92(b)(3).

Example 1

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

	INCREASE IN RISK	DECREASE /EQUIVALENT RISK
INCREASE/ EQUIVALENT BENEFIT	<div style="border: 1px solid #0070c0; border-radius: 10px; padding: 10px; text-align: center;"> Conducting a benefit-risk assessment is recommended. </div>	
DECREASE IN BENEFIT		

Is a benefit-risk assessment recommended?

Yes. A benefit-risk assessment is recommended to assess the increase in risk and increase in benefit.

Example 1 continued...



Benefits:

- The new device, condom fabricated from synthetic material, provides another option for contraception and prophylaxis, which is particularly beneficial for users and their partners who are allergic to natural rubber latex.

Risks:

- The clinical study showed that the occurrence of slippage was slightly higher. Increase in slippage increases the risk of undesired pregnancy and/or transmission of sexually-transmitted infections (STIs).

Additional Factors:

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

	INCREASE IN RISK	DECREASE /EQUIVALENT RISK
INCREASE/ EQUIVALENT BENEFIT	Conducting a benefit-risk assessment is recommended.	
DECREASE IN BENEFIT		

Example 1 continued...

SE Analysis:

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

	INCREASE IN RISK	DECREASE /EQUIVALENT RISK
INCREASE/ EQUIVALENT BENEFIT		
DECREASE IN BENEFIT		

Example 2



Scenario: A self-contained device uses a **low-level laser therapy for the treatment of toenail fungus (onychomycosis)**. The new device uses:

- **A different wavelength than the predicate device**
- **Wavelength produces different photo-biological effects**
- **Has a power level that much lower than the predicate device**
- **Has a constant energy delivery sequence in comparison to the pulsing sequence of the predicate device.**

For the treatment of onychomycosis, the purported mechanism of action is either a **photo-biological** process in which the laser wavelength interacts with chromophores within the fungal cells resulting in cell death or may involve a **thermal effect** on the fungal cells at temperatures below those required for tissue coagulation or tissue vaporization.

- **Due to the differences in technological characteristics and possible changes in principles of operation between the new device and predicate device, the manufacturer provided clinical data to compare their device to the predicate device.** The device would have equivalent benefit as the predicate device if it had a comparable amount of responders. A responder is a subject whose toenail is effectively treated according to predefined success criteria. **The clinical data demonstrated that the responder rate was lower in the group treated with the new device. However, the new device posed a lower risk than the predicate device because of the lower power level.**

	INCREASE IN RISK	DECREASE /EQUIVALENT RISK
INCREASE/EQUIVALENT BENEFIT		
DECREASE IN BENEFIT		Conducting a benefit-risk assessment is recommended.

Is a benefit-risk assessment recommended?

Yes. A benefit-risk assessment is recommended to assess the decrease in risk and decrease in benefit.

Example 2 continued...



Benefits:

The new device offers an alternative treatment modality than the predicate device. However, the study failed to meet the primary endpoint because it showed a lower responder rate.

Risks:

Reduction in power in the new device offers lower risk in comparison to the predicate device due to the minimal side effects.

Additional Factors:

- **Uncertainty:** There were significant data inconsistencies regarding the manufacturer's photographs and data set in comparison to the predicate device thus, raising significant concerns regarding the reliability of the data.
- **Risk mitigation:** Wearing of laser safety protective glasses to prevent accidental eye damage from laser exposure.

	INCREASE IN RISK	DECREASE /EQUIVALENT RISK
INCREASE/ EQUIVALENT BENEFIT		
DECREASE IN BENEFIT		Conducting a benefit-risk assessment is recommended.

Example 2 continued...

SE Analysis:

- The clinical data failed to demonstrate that the new device provided benefit for the majority of treated patients.
- Although the new device imparts less risk, the benefit of the device is considerably smaller than the predicate device.
- Data provided presented significant inconsistencies and was considered to be unreliable.
- Overall, due to the level of uncertainty and the relatively small benefit observed, this device would likely be found NSE based on lack of adequate performance data.

	INCREASE IN RISK	DECREASE /EQUIVALENT RISK
INCREASE/ EQUIVALENT BENEFIT		
DECREASE IN BENEFIT		<div style="border: 1px solid gray; border-radius: 10px; padding: 10px; text-align: center;"> Conducting a benefit-risk assessment is recommended. </div>



Key Message

- **Purpose of the 510(k) Benefit-Risk Guidance**

Intended to serve as an aid for evaluating the benefit-risk profile of a new device especially when there are differences in the benefit-risk profile of a new device when compared to a predicate device.

- **Understand when a benefit-risk assessment is performed in a 510(k)**

When there is:

- 1) an increase in risk and increase or equivalent benefit or
 - 2) a decrease in benefit and a decrease or equivalent risk
- when comparing a new device to a predicate device.

- **The benefit risk profile of a new device does not have to be identical to that of a predicate device**

FDA assesses the differences between the benefit-risk profile of a new device and a predicate device. This assessment informs the final substantial equivalence decision.

Link to Final 510(k) Benefit-Risk Guidance:

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

Link to Certain Pre-Existing Guidance Documents:

- [Deciding When to Submit a 510\(k\) for a Change to an Existing Device](#)
- [The 510\(k\) Program: Evaluating Substantial Equivalence in Premarket Notifications \[510\(k\)\]](#)
- [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](#)



Questions?

Email 510(k) Program mailbox
510k_Program@fda.hhs.gov

For general questions, email the Division of Industry and Consumer Education: DICE@fda.hhs.gov

Slide Presentation, Transcript and Webinar Recording will be available at:

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

Under Heading: How to Study and Market Your Device; In the section: Premarket Notification (510k)

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