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Webinar Topics

Early Feasibility Study (EFS) Investigational Device Exemptions

A Valuable Regulatory Tool for Medical Device Development

New FDA Draft Guidance

"FDA Categorization of Investigational Device Exemption (IDE) Devices to Assist the Centers for Medicare and Medicaid Services (CMS) with Coverage Decisions"

Early Feasibility Study (EFS) Investigational Device Exemptions

A Valuable Regulatory Tool for Medical Device Development

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Agenda

- **What an Early Feasibility Study is**
  - How it can benefit sponsors
- **Key Elements of the EFS Guidance Document**
  - What does doing the "right testing at the right time" mean?
- **What a successful pathway to an EFS IDE approval looks like**
- **Common questions/tips**
- **Helpful links**

What an EFS IDE is

IDE - Investigational Device Exemption

- An IDE submission allows an investigational device to be used in a clinical study in order to collect safety and effectiveness data.

EFS IDE - A standard IDE except…

- There are significant unknowns about how the device will perform
  - Device is generally early in development or
  - Device has a new intended use
- Small number of subjects in the clinical investigation
  - Initial evaluation of safety and/or effectiveness
  - Proof of concept

**** EFS is an informal designation***

How Conducting an EFS in the US Benefit Sponsors

Permits A More Efficient Pathway to US Commercialization

- FDA feedback early in product development may…
  - Help the sponsor improve their development strategy and reduce the chances that unnecessary testing is completed.
  - Increase the predictability of data requirements for a future study or commercialization needs.
- Data collection in the US patient population may be easier to leverage to support later studies.

How Conducting an EFS in the US Benefit Sponsors

Additional Benefits

- Assurance of patient protection under the IDE regulations
- Have better access to technical experts and Key Opinion Leaders in the US
- Logistical advantage and proximity to US innovation centers
- Allows for device iteration, including during the EFS study, which may result in high quality products

Some Types of IDE studies

EFS	Feasibility	Pivotal
Small number of patients, < 15 (approximate)	More patients than EFS	Number of patients determined by statistical needs
➢ ***There are fundamental questions about device performance & safety*** ➢ Device design may change. ➢ There may be limited nonclinical data available	Enough is known about the design, procedure or indication to justify clinical studies with more patients than EFS	Device is the final design and there is significant information known about the design, procedure and indication.
Purpose of study can be… ➢ to demonstrate a proof of concept ➢ determine what design or procedure changes could optimize the therapy ➢ And more…	Purpose of study can be… ➢ capture preliminary safety and effectiveness information and to adequately plan an appropriate pivotal study	Purpose of study can be… ➢ Demonstrate safety and effectiveness to support a marketing application

*note: not all of these phases are required for market approval

Key Elements of the EFS Guidance

- **Doing the "Right Testing at the Right Time"**
  - Comprehensive testing during early phases of device development may add cost without significant return (some testing may be deferred)
  - *EFS is not to take the place of informative nonclinical testing*
- **Unknowns and risk can be addressed by…**
  - Using clinical mitigations to provide patients with extra protection
  - The use of more frequent/detailed reporting
  - Informed consent recommendations

Key Elements of the EFS Guidance continued…

- **Allows for timely device and clinical protocol changes**
  - More changes can be made during the study through 5-day notification rather than FDA approval
  - Contingent approval: approval of anticipated or proposed device changes can be obtained contingent on the completion of an agreed upon test plan and acceptance criteria
- **Recommendations on pre-submission contents is provided**
  - An example risk assessment method is provided

What Does Doing the "Right Testing at the Right Time" Mean?

FDA Recognizes the Value of Alternative Nonclinical Test Methods and Leveraging Data

- **Different test methods for small batches**
  - E.g. – Single lot Ethylene Oxide sterilization versus full Ethylene Oxide sterility validation
- **Some test data could be leveraged. Examples…**
  - Some biocompatibility endpoints could be leveraged from an animal study if one is conducted.
  - Some test data could be leveraged from a previous version of the device.

FDA Recognizes That Some Nonclinical Testing Could be Deferred

Risk presented to patient (after clinical mitigations are considered) versus potential benefit.

- **Is the probability of failure or patient harm understood and can this be mitigated?**

  (e.g. risk of irritation to a material, possible mitigation = timely clinical assessments/interventions)

- **Can a potential failure/harm be detected and mitigated?** (e.g. risk of patient pain, possible mitigation = titrating therapy, ability to revert to standard of care)

Considerations for Deferral of Nonclinical Testing Continued…

- **Can the clinical study be controlled to further protect patients?**

  (e.g. limiting use of a device to the hospital instead of the home, where it may eventually be used, may change EMC testing needs)

- **Is the clinical situation emergent and/or are there are no alternatives available?**

  (e.g. long term durability testing deferred due to the criticality of short term benefit)

Considerations for Deferral of Nonclinical Testing Continued…

- **Will the nonclinical test data provide valuable information on how the device will perform in the proposed clinical study?**

  (E.g. If test data will not inform the clinical study today but will characterize the device and will be important for developing specifications prior to a marketing approval, data could be gathered in parallel with the clinical study and submission of this data to FDA could be deferred.)

Note: If the clinical situation is non-emergent and there are therapeutic alternatives, the amount of nonclinical testing may need to be comparable to other available therapies.

Understanding and Explaining the Utility of the Nonclinical Tests is Important

- If it is an animal study, which device performance data will inform the human clinical study?
- Is the test conservative or not?
- Is the test validated?
- Does the test have historical value?
- Will the data be used for quality control in the future?

➢ What will the data tell us? Are there options to protect patients when nonclinical testing has limited utility?

What a Successful Pathway to an EFS IDE Approval Looks Like

Recommendation #1

Sponsor is Well Prepared

- Sponsor knows what information they want to learn from the EFS
- Sponsor uses their resources: FDA guidance documents and recognized standards, CDRH Learn Modules, external experts
- Sponsor has reached out to an EFS representative to discuss their submission strategy

Recommendation #2

Submissions are well planned

- Informational meeting may be useful, for novel ideas in particular
- Initial pre-sub includes all the information described in the guidance (Goal: agree upon the risks and test plan)
- Additional pre-subs as needed (ex: if test requirements are uncertain/discuss clinical protocol)
- IDE submission contains all required information

Note:

The use of pre-submissions to discuss the test plan and the clinical protocol…

- Can be useful when the nonclinical testing needed is unclear, can be used to agree upon the test plan that will support an IDE submission with FDA
- May avoid the need to re-do expensive and time consuming testing
- May help determine appropriate clinical mitigations, reporting requirements and the patient population for whom the benefit-risk profile supports inclusion into the EFS

Highly Recommended

Recommendation #3

Submissions are high quality

- Contain enough information for FDA to provide valuable feedback.
  - Reference the EFS Guidance and IDE required elements (links are located at the end of this presentation)
- Contents are well organized and navigable.
- High quality scientific discussion and evidence is provided.

Recommendation #4

The sponsor is able to describe why additional nonclinical testing will not be informative and that a human clinical study is appropriate.

- There is a clear identification of potential risks & how they will be addressed
  - Nonclinical testing, clinical mitigations, reporting
- Explanation is provided for why the plan is sufficient:
  - Explain what can/cannot be learned from bench tests/animal models and why any information to be leveraged is directly applicable to the study
- List which tests will be done to support the EFS versus which will be done to support a later study if applicable

Common Questions

Question #1

Is EFS for Novel Technology Only?

NO: EFS are just small studies used to gather information when there are significant unknowns.

EFS May be Used for a Variety of Reasons

- To study a novel device
- To study an expanded access (e.g. for devices used for compassionate use or emergency use cases)
- To support new indications for a marketed device

When is a good time to talk to FDA about an EFS?

After…

- You have established your general device design, intended use and what information you would like to gather from the EFS

Before…

- Expensive and time consuming nonclinical testing has been started

➢ It is recommended to communicate with FDA informally throughout the development process to optimize submission efficiency

The guidance document contains an optional risk assessment template. When / How is this used?

Called a "Device Evaluation Strategy (DES) Table"

- Can be helpful if you do not currently use another method for assessing risk (e.g. ISO standard).
- Should contain a **high level** description of risks, not as detailed as an FMEA. More from a clinician's perspective.
- Intent is to link primary risks together with risk mitigations.

Tips

Tips

1. **If you are iterating your device, keep samples of previous generations.**
   - They may be useful in the future for establishing biocompatibility equivalence, for example.

2. **Keep clear and detailed records of the testing completed with each device iteration.**
   - Ensure that a detailed description of the device iteration is included in protocols.
   - This may help leverage information in future submissions.

Tips

3. **If you would like to use test results that were not obtained per standard FDA recommendations, we recommend that you provide an explanation for why the data is sufficient.**

   - E.g. If your animal study is intended to support device safety and deviates from 21 CFR 58 (Good Laboratory Practices) we recommend that you tabulate each part of the regulations, list how the study deviates and how you will ensure data integrity and minimize bias.

Note: Only animal studies intended to support device safety need to address 21 CFR 58. Reference FDA guidance "The Applicability of Good Laboratory Practice in Premarket Device Submissions: Questions & Answers" for further information.

Tips

If your animal study is intended to support device safety and deviates from GLP, FDA recommends that it include…

- Protocol signed/dated by all key parties prior to initiation of the study
  - Including objectives, acceptance criteria, and detailed procedures
  - Include IACUC protocol with amendments
  - Clear description of the animals enrolled in the study and their final designation
- Quality measures and an explanation of how data integrity is ensured. QA personnel to monitor the study - may be in the same company but organizationally separate and independent of those engaged in the study.
- Animal facility licenses, accreditations, and assurances

Note: Reference FDA guidance on EFS and the draft guidance "General Considerations for Animal Studies for Medical Devices" for further information.

Tips

4. **Understand that FDA feedback is not a directive.** It is information for your consideration and to assist with further discussion.

Helpful Links

- **Early Feasibility Study Guidance**
  http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM279103.pdf2
- **EFS CDRH Learn Modules**
  http://www.accessdata.fda.gov/cdrh_docs/presentations/EFS/story.html
- **Pre-Submission Guidance**
  http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM311176.pdf
- **IDE Submission Information**
  http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/InvestigationalDeviceExemptionIDE/ucm046706.htm#reqele
- **Design Controls Guidance**
  http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070627.htm
- **Electronic Submissions Guidance**
  http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM313794.pdf

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Questions?

Want to share your EFS experience & thoughts for Improvement? Contact Carla Wiese, Policy Analyst for the Early Feasibility Program - 301-796-0627 or Carla.wiese@fda.hhs.gov

General questions about early feasibility studies? Contact CDRH's Division of Industry and Consumer Education (DICE) at dice@fda.hhs.gov, 1-800-638-2041, or 301-796-7100

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Under "How to Study and Market Your Device" Heading

New FDA Draft Guidance

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Agenda

- Why IDEs are conducted and why they are categorized
- Why there is new guidance related to CMS categorization
- What the changes are between the old policy and the new policy
- Considerations when changing from Category A to B
- How a category designation may affect coverage in a study
- Other factors that may impact coverage

Why Are IDE Studies Conducted?

An investigational device exemption (IDE) allows an investigational device to be used in a clinical study in order to collect safety and effectiveness data.

- FDA approval of an IDE submission indicates FDA has determined:
  - The sponsor has provided adequate data to support initiation of the study.
  - There are no subject protection concerns to preclude initiation of the study after IRB approval.
  - Benefit-risk profile for the study is favorable.

Reference: 21 CFR 812

Why Are IDE studies Conducted? Continued…

Generally, an IDE study is conducted to answer outstanding questions about safety and effectiveness.

However, the extent to which initial questions of safety and effectiveness are already addressed depends on many factors.

Why IDEs Are Categorized

- **An Interagency Agreement (IA) between CMS and the FDA was made in 1995 to support CMS' decision making for coverage. As part of this agreement, FDA assigns a device with an FDA approved IDE to one of two categories:**
  - Experimental/Investigational (Category A)
  - Non-experimental/Investigational (Category B)

- **This agreement allowed for expanded coverage to include some investigational devices.**

Why IDEs Are Categorized

- The category designation was to be based on the extent to which "initial questions of safety and effectiveness" have been answered.
- Specific criteria were defined in the 1995 IA for how FDA would determine the appropriate category.
- The categorization has been used by CMS as part of its determination of whether or not items and services meet the requirements for Medicare coverage.

Why There is New Guidance Related to CMS Categorization

1) The previous FDA policy regarding categorization did not adequately articulate criteria that are relevant to certain studies such as feasibility studies.
2) The previous policy did not contain sufficient guidance regarding how a category designation may change from A to B.
3) The previous criteria did not consider all regulatory pathways. (e.g. de novo submission)

Additional Factors

CMS changed from local Medicare Administrative Contractor review and approval of IDE studies to a centralized review and approval of IDE studies effective January 1, 2015.

Interactions between FDA and CMS since that time have highlighted a need for changes to categorization in order to improve consistency.

	1995 Interagency Agreement	Draft Guidance
Changes	Detailed criteria were used to designate an IDE device category.	Criteria have been simplified to ensure that devices fall into the correct category.
Changes	Limited or no visibility to how a category change may occur as knowledge is gained.	Draft guidance provides an explanation of how a category change may occur.
Changes	No examples provided.	Examples provided.
The same	FDA review team makes the category designation.	Unchanged
The same	Category designation is to be based on the degree to which initial questions of safety and effectiveness are resolved.	Unchanged
The same	The categorization will then be used by CMS as part of its determination of whether or not items and services will be covered.	Unchanged

Draft Guidance

Draft guidance is proposed documentation not yet ready for implementation.

Issuance Date: June 1, 2016

Comment period closes: August 1, 2016

www.regulations.gov

docket # FDA-2016-D-1159

Regulatory Context: Category A

Category A: Experimental

42 CFR 405.201(b):

"…a device for which 'absolute risk' of the device types has not been established (that is, initial questions of safety and effectiveness have not been resolved) and the FDA is unsure whether the device type can be safe and effective."

Proposed Criteria: Category A

FDA intends to consider a device to be in Category A if one or more of the following criteria are met:

1. **No PMA approval, 510(k) clearance or de novo request has been granted for the proposed device or similar devices, and non-clinical and/or clinical data on the proposed device do not resolve initial questions of safety and effectiveness.**

Proposed Criteria: Category A

2. The proposed device has different characteristics compared to a legally marketed device; and information related to the marketed device does not resolve initial questions of safety and effectiveness for the proposed device. Available non-clinical and/or clinical data on the proposed device also do not resolve these questions.

Proposed Criteria: Category A

3. The proposed device is being studied for a new indication or new intended use for which information from the proposed or similar device related to the previous indication does not resolve initial questions of safety and effectiveness. Available non-clinical and/or clinical data on the proposed device relative to the new indication or intended use also do not resolve these questions.

Category A Example

A device is completely novel and has no, or limited, previous human use and there are initial questions of safety and effectiveness. There is adequate non-clinical information to support initiation of an early feasibility study that will provide data to inform potential device design or procedural improvements.

Category A Example

An already approved or cleared device is being evaluated for a new intended use or indication wherein the device will be placed in a different anatomical location.

The device's technology is unchanged from what was initially approved; however, it is uncertain as to whether the device can be safely placed in the new anatomical location and whether the device can also be effective in the new anatomical location. Therefore, there are inadequate data to resolve the initial questions of safety and effectiveness relative to the new intended use or indication.

Regulatory Context: Category B

Category B: Nonexperimental/Investigational

42 CFR 405.201(b)

"…a device for which the incremental risk is the primary risk in question (that is, initial questions of safety and effectiveness of that device type have been resolved), or it is known that the device type can be safe and effective because, for example, other manufacturers have obtained FDA premarket approval or clearance for that device type."

Proposed Criteria: Category B

FDA intends to consider a device to be in Category B if one or more of the following criteria are met:

1. **No PMA approval, 510(k) clearance or de novo request has been granted for the proposed device or similar devices; however, available clinical data (e.g., feasibility study data) and/or non-clinical data for the proposed device or a similar device resolve the initial questions of safety and effectiveness.**

Proposed Criteria: Category B

2. The proposed device has similar characteristics compared to a legally marketed device, and information related to the marketed device resolves the initial questions of safety and effectiveness for the proposed device. Additional non-clinical and/or clinical data on the proposed device may have been used in conjunction with the leveraged information to resolve these questions.

Proposed Criteria: Category B

3. The proposed device is being studied for a new indication or new intended use; however, information from the proposed or similar device related to the previous indication resolves the initial questions of safety and effectiveness. Additional non-clinical and/or clinical data on the proposed device may have been used in conjunction with the leveraged information to resolve these questions.

Category B Example

Adequate data have been gathered from non-clinical testing and the clinical results of a feasibility study such that initial questions of safety and effectiveness have been resolved. A pivotal study will be initiated to provide the primary clinical evidence for the safety and effectiveness of the device in support of a future marketing application.

Category B Example

An approved device will be evaluated for a new indication.

Data exist on the approved device for another similar indication, and non-clinical data have also been supplied such that the initial questions of safety and effectiveness related to the new indication have been resolved. The new study to be conducted will provide further data regarding device performance for this new indication.

When Are IDEs Categorized?

The FDA review team will make a categorization decision at the time of the first approval (full or conditional) of an IDE study.

A categorization change will be considered for study expansion or upon a request for re-designation.

The category is included in FDA's approval letter for the IDE.

Information That May Support a Category Change

- Nonclinical test data
- External data on the technology (e.g. data from other similar devices)
- Preliminary clinical data on the device

Example of a Change From Category A to B

Adequate data have been gathered on a device from non-clinical testing, the completion of an early feasibility study within the United States (US), as well as a small non-US clinical study such that initial questions of safety and effectiveness have been resolved. Additional data are needed to help inform a pivotal study design; therefore, a traditional feasibility study will be initiated.

Although the early feasibility study was originally designated as Category A, adequate data as described above have since been gathered to support a change to Category B for the traditional feasibility study.

How a Categorization Designation May Affect Coverage in a Study

- If the study is designated Category A: the device may not be covered but routine care and services may be covered.
- If the study is designated Category B: then the device and routine care and services may be covered.

Other Factors That May Affect Coverage in a Study

- Has a previous national coverage decision been made for the device type and/or procedure?
  - A coverage decision may supersede the category designation.
- Will the device be adjunctive to a procedure in which a coverage decision has been made?
  - A coverage decision may supersede the category designation.
- Is the device relevant to the Medicare population?
- Have other CMS criteria been met (reference the CMS website link at the end of this presentation)?
- Others…

Links

Link to the FDA Draft Guidance

"FDA Categorization of Investigational Device Exemption (IDE) Devices to Assist the Centers for Medicare and Medicaid Services (CMS) with Coverage Decisions"

- http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm504091.pdf

Link to a CMS website

"Medicare Coverage Related to Investigational Device Exemption (IDE) Studies"

- https://www.cms.gov/medicare/coverage/IDE/index.html

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