

# Draft Guidance for Industry, Clinical Investigators, Institutional Review Boards, and Food and Drug Administration Staff

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## FDA Decisions for Investigational Device Exemption (IDE) Clinical Investigations

### *DRAFT GUIDANCE*

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For questions regarding this document, contact (CDRH) Owen Faris, 301-796-6356 or [Owen.Faris@fda.hhs.gov](mailto:Owen.Faris@fda.hhs.gov) or (CBER) Office of Communication, Outreach and Development at 1-800-835-4709 or 301-827-1800.



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

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## FDA Decisions for Investigational Device Exemption (IDE) Clinical Investigations

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### 1 Introduction and Scope

FDA seeks to encourage medical device research and innovation to address important clinical needs and improve patient care. In many cases, device development and evaluation includes clinical investigation. This guidance document has been developed to promote the initiation of clinical investigations to evaluate medical devices under FDA's Investigational Device Exemptions (IDE) regulations, Title 21 Code of Federal Regulations (CFR) Part 812.

FDA approval of an IDE submission allows the initiation of a clinical investigation of a significant risk<sup>1</sup> device. This guidance is intended to provide clarification regarding the regulatory implications of the decisions that FDA may render based on review of an IDE and to provide a general explanation of the reasons for those decisions.

In an effort to promote timely initiation of clinical investigations in a manner that protects study subjects, FDA has developed methods to allow a clinical investigation of a device to begin under certain circumstances, even when there are outstanding issues regarding the IDE submission. These mechanisms, including approval with conditions, staged approval, staged

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<sup>1</sup> 21 CFR 812.3(m): A *significant risk device* means an investigational device that:

- (1) Is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject;
- (2) Is purported or represented to be for a use in supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a subject;
- (3) Is for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a subject; or
- (4) Otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.

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approval with conditions, and communication of outstanding issues related to the IDE through *future considerations*, are described in this guidance.<sup>2</sup>

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances 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 guidances means that something is suggested or recommended, but not required.

## **2 IDE Decisions**

FDA's regulations describe FDA actions on an IDE:

(a) *Approval or disapproval*. FDA will notify the sponsor in writing of the date it receives an application. FDA may approve an investigation as proposed, approve it with modifications, or disapprove it. An investigation may not begin until:

(1) Thirty days after FDA receives the application at the address in 812.19 for the investigation of a device other than a banned device, unless FDA notifies the sponsor that the investigation may not begin; or

(2) FDA approves, by order, an IDE for the investigation<sup>3</sup>

Thus, FDA's regulations provide for three FDA actions on IDE applications:

- Approval
- Approval with Conditions<sup>4</sup>
- Disapproval

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<sup>2</sup> This guidance does not offer specific information related to the design of a clinical investigation, nor does this guidance discuss the specific content that should be provided in an IDE application. For additional information on those topics, please refer to FDA's regulations (21 CFR 812.20 and 812.25) and to FDA's Guidance on IDE Policies and Procedures

(<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080202.htm>).

<sup>3</sup> 21 CFR 812.30.

<sup>4</sup> FDA has traditionally referred to IDE approvals that have conditions as "Conditional Approvals." FDA believes that the term "Approval with Conditions" is more appropriate because the term conveys that the IDE has been approved and may begin without awaiting further FDA review.

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FDA must inform the sponsor<sup>5</sup> or sponsor-investigator<sup>6</sup> of its decision, or must notify the sponsor that the investigation may not begin, within 30 days from the date of receipt of the IDE application, or the IDE application will be deemed approved. If an IDE application is approved or approved with conditions, the sponsor may begin subject enrollment with the number of subjects and investigational sites specified in FDA's decision letter upon receipt of Institutional Review Board (IRB) approval; the IRB approval may occur prior to FDA approval.

If FDA does not have outstanding issues that must be addressed to support the study of the subject cohort under the proposed investigational plan, then the IDE will be approved *without* conditions<sup>7</sup>. Alternatively, if FDA has identified issues that must be addressed but do not preclude initiation of the clinical investigation, the IDE will be approved *with* conditions. In the case of approval with conditions, approval is granted on the condition that, within a specified timeframe from the date of FDA's decision letter, usually 45 days<sup>8</sup>, the sponsor submits information addressing the issues identified in FDA's letter. Examples of the types of issues that may be identified in an approval with conditions letter are discussed later in this document. In certain instances, resolution of outstanding issues before subject enrollment may be necessary. In these instances, the IDE will be disapproved, meaning that the sponsor may not initiate enrollment in the clinical investigation until the sponsor responds to the issues identified in FDA's letter and receives an approval or approval with conditions letter.

### **3 IDE Approval**

If FDA approves an IDE application and IRB approval is obtained, the sponsor may begin subject enrollment in accordance with the limits described in FDA's decision letter, including the maximum number of subjects and investigational centers. FDA will approve an IDE application without conditions when the IDE sponsor has submitted data and an adequate clinical investigation plan that support initiation of the study in humans. This assessment is based primarily on FDA's review of the considerations discussed in Section 8 of this document, in addition to other issues specific to the application.

In some cases, FDA may determine that an outstanding issue remains but that the IDE application can still be approved and the issue can be addressed with data that will be gathered in parallel with the enrollment of some portion of study subjects (i.e., staged approval). In other cases, FDA may inform the sponsor of an issue that FDA believes should

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<sup>5</sup> 21 CFR 812.3(n): *Sponsor* means a person who initiates, but who does not actually conduct, the investigation, that is, the investigational device is administered, dispensed, or used under the immediate direction of another individual. A person other than an individual that uses one or more of its own employees to conduct an investigation that it has initiated is a sponsor, not a sponsor-investigator, and the employees are investigators.

<sup>6</sup> 21CFR 812.3(o): *Sponsor-investigator* means an individual who both initiates and actually conducts, alone or with others, an investigation, that is, under whose immediate direction the investigational device is administered, dispensed, or used. The term does not include any person other than an individual. The obligations of a sponsor-investigator under this part include those of an investigator and those of a sponsor.

The remainder of this document uses the term "sponsor" for both sponsor and sponsor-investigator.

<sup>7</sup> The term "approval" in this document and in FDA's communications means approval without conditions.

<sup>8</sup> The remainder of this document references 45 days as the specified timeframe.

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be considered in preparation for a marketing application or a future clinical investigation (i.e., future consideration). These options are discussed in Sections 5 and 6, respectively, of this document.

## **4 IDE Approval with Conditions**

If FDA approves an IDE application with conditions, the sponsor may begin subject enrollment upon receipt of IRB approval on the condition that, within 45 days from the date of FDA's decision letter, the sponsor submits information addressing the issues identified in FDA's letter. An IDE may be approved with conditions if FDA has determined, despite outstanding issues, that the information provided is sufficient to justify human clinical evaluation of the device, and that the proposed study design is generally acceptable. Previously known as "conditional approval," the phrase "approval with conditions" will now be used to convey that the outstanding issues do not raise concerns that preclude FDA from granting approval for initiation of the clinical investigation. Therefore, resolution of those issues is not required prior to initiation of enrollment in the study, with exception of issues related to the informed consent document. If FDA identifies issues with an informed consent document, those issues must be addressed before enrollment begins in order to ensure that informed consent is obtained in accordance with 21 CFR Part 50 - Protection of Human Subjects. Outstanding issues that may lead to approval with conditions include:

- Issues related to data analysis methods and handling if the corrections will occur prior to the gathering of important study data;
- Issues related to late stage follow-up procedures and assessments, if the corrections are made prior to beginning any late-stage procedures or assessments;
- Minor divergences from what FDA considers appropriate study endpoints, design assumptions, or key definitions;
- Issues related to the informed consent document that must be corrected before enrolling subjects but can be reviewed by FDA after study initiation;
- Requests for additional information or data involving non-clinical testing issues that do not need to be resolved prior to study initiation;
- Other minor clarifications, corrections, or modifications that do not need to be resolved prior to review completion.

The sponsor must submit a supplement<sup>9</sup> to the IDE to respond to the issues raised in FDA's approval with conditions letter, usually within 45 days; otherwise, the IDE will be disapproved. See 21 CFR 812.30(b). For each issue identified in FDA's letter, an acceptable response provides the specific information or modification(s) requested by FDA. In some cases, the sponsor may choose to provide a scientifically valid alternative to FDA's request or to provide a scientifically valid rationale for why the information or modification(s) is not needed. FDA will inform the sponsor of its decision within 30 calendar days from the date of receipt of the supplement. If FDA determines that the issues have been adequately resolved, FDA will grant approval without conditions. However, if any issues remain, FDA may again

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<sup>9</sup> Once an IDE is approved or approved with conditions, subsequent submissions to FDA related to the IDE are designated as "IDE supplements."

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grant approval with conditions and will communicate the remaining outstanding issues to the sponsor by letter. In this case, the sponsor may continue to enroll subjects in the study on the condition that, within 45 days, the sponsor responds to the remaining issues identified in FDA's letter. In some cases, a sponsor's unsatisfactory response to FDA's questions could result in FDA withdrawing approval of the IDE.

## **5 Staged Approval or Staged Approval with Conditions**

This guidance defines a process, termed "staged approval" or "staged approval with conditions"<sup>10</sup> by which FDA may grant IDE approval or approval with conditions, while certain outstanding questions are answered in parallel with enrollment in the clinical investigation. Staged approval and staged approval with conditions permit the clinical investigation to begin in a timely manner while maintaining appropriate subject protections.

Under staged clinical investigations, FDA will grant approval or approval with conditions for a subset of the planned subject cohort while the particular outstanding questions are addressed. If FDA and the sponsor have agreed to the additional data that will be provided and there are no other outstanding issues to be addressed (i.e. under approval with conditions), a staged clinical investigation can receive approval without conditions, with enrollment limited to the number of subjects to be enrolled in the first stage. The size of the enrollment stages and the timing for the reporting of additional information should ideally be designed so that study enrollment does not need to be halted during the trial if the data submitted to address the outstanding issue(s) are acceptable. The sponsor will be permitted to expand enrollment once an IDE supplement, which includes the necessary additional information, is submitted to FDA for review and found to be acceptable.

A staged clinical investigation may be appropriate in the following situations:

- FDA believes it is necessary to obtain clinical confirmation of the safety profile of a device or the potential for benefit by reviewing the data from subjects enrolled early in the clinical investigation before exposing the entire subject cohort to the risks of the device and the clinical investigation.
- Information has been provided that is sufficient to justify enrollment of a portion of the subjects in the clinical investigation. However, long-term non-clinical testing is also required and will be conducted in parallel with early enrollment in the clinical investigation. The results of the long-term non-clinical testing can be validated before FDA permits enrollment of the entire subject cohort.

Staged approval or staged approval with conditions is most common for pivotal studies<sup>11</sup> (i.e., studies that are designed to provide the primary clinical evidence to support a marketing application) in which many subjects will be enrolled over an extended period of time, but

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<sup>10</sup> The remainder of this section will use the term "staged approval" to refer to staged approval and staged approval with conditions.

<sup>11</sup> Pivotal studies are discussed in more detail in the FDA draft guidance titled, "Design Considerations for Pivotal Clinical Investigations for Medical Devices" (available at [www.fda.gov/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm265553.htm](http://www.fda.gov/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm265553.htm)).

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may be applicable to other clinical investigations as well. Some additional considerations that are specific to staged pivotal studies include:

- Successful support of a marketing application under staged approval is not expected until the full planned cohort of subjects is studied.
- A staged pivotal study should only be considered if the additional information that is requested is not expected to result in changes to important elements of the clinical investigation (e.g., endpoints, sample size, stopping rules) or device design. If the information is expected to result in changes to important elements of the trial or device design, then a separate feasibility<sup>12</sup> study may be more appropriate. In some cases, prospectively defined adaptive design techniques may allow for a pivotal study to accommodate pre-planned study changes based on data gathered early in the study without the need for additional feasibility data.
- If FDA determines that new feasibility data are needed prior to approval of the proposed pivotal IDE that was submitted for review, FDA may choose to grant approval of the IDE for a limited number of subjects on the condition that the sponsor considers the study to be a feasibility study rather than a pivotal study. The data from the feasibility study may be used to inform the design and support IDE approval for a future pivotal study.
- The data requested by FDA should not inappropriately unblind any of the relevant stakeholders, including the sponsor, investigators, or study management personnel, to critical study data. If the data that are needed will necessarily unblind these stakeholders to critical study elements, then a feasibility study may be more appropriate to answer these questions.

## **6 Future Considerations in Approval, Approval with Conditions, or Disapproval Letters**

Future considerations are issues or recommendations communicated in an approval, approval with conditions, or disapproval letter that FDA believes the sponsor should consider in preparation for a marketing application or a future clinical investigation. Future considerations are intended to provide helpful advice to sponsors regarding important elements of the future application that the IDE may not specifically address. Examples of typical future considerations include discussion of:

- Known limitations of the IDE clinical investigation with regard to supporting certain claims or indications. For example, FDA may remind the sponsor that due to a specific exclusion criterion, any approved Indication for Use based on the clinical investigation may be limited to that particular population rather than a broader population.
- Potential limitations of the IDE that depend on currently unknown variables. For example, if FDA believes that the sponsor may have slightly overestimated the effect

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<sup>12</sup> Feasibility studies are developmental studies that are not intended to provide the primary clinical evidence to support a marketing application. A draft guidance document entitled “Investigational Device Exemptions (IDE) for Early Feasibility Medical Device Clinical Studies, Including First in Human (FIH) Studies,” discusses the types of feasibility studies.

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of the device relative to the control, FDA may wish to advise the sponsor that the clinical investigation may be underpowered to achieve its goals<sup>13</sup>. In such a case, before beginning the study, the sponsor may wish to consider submitting a protocol modification for FDA's review to revise the treatment effect assumptions and sample size calculations or to use an adaptive study design to allow for pre-specified sample size adjustments to be made if the original assumptions are incorrect. Once study data have been gathered, such changes may no longer be appropriate.

- Specific analyses that FDA will expect to see in the marketing application. For example, if the clinical investigation is being conducted in US and non-US populations, FDA may wish to inform the sponsor that FDA will expect to receive analyses demonstrating that the US and non-US data can be pooled.
- Specific non-clinical testing that, while not necessary to support approval of the IDE, will be needed to support the marketing application. For example, FDA may have accepted shorter term device durability testing to support IDE approval but may wish to remind the sponsor that longer term testing will be needed to support a marketing application.

## **7 IDE Disapproval**

If an IDE application is disapproved, the sponsor may not initiate the clinical investigation until the sponsor submits an amendment<sup>14</sup> to the IDE to respond to the deficiencies identified in FDA's letter and subsequently receives a new letter from FDA granting approval or approval with conditions. There are five major reasons why FDA may disapprove an IDE, as discussed in 21 CFR 812.30(b):

*(b) Grounds for disapproval or withdrawal. FDA may disapprove or withdraw approval of an application if FDA finds that:*

- (1) There has been a failure to comply with any requirement of this part or the act, any other applicable regulation or statute, or any condition of approval imposed by an IRB or FDA.*
- (2) The application or a report contains an untrue statement of a material fact, or omits material information required by this part.*
- (3) The sponsor fails to respond to a request for additional information within the time prescribed by FDA.*
- (4) There is reason to believe that the risks to the subjects are not outweighed by the anticipated benefits to the subjects and the importance of the knowledge to be gained, or informed consent is inadequate, or the investigation is scientifically unsound, or there is reason to believe that the device as used is ineffective.*
- (5) It is otherwise unreasonable to begin or to continue the investigation owing to the way in which the device is used or the inadequacy of:*
  - (i) The report of prior investigations or the investigational plan;*

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<sup>13</sup> If the available information strongly indicate that the study will be underpowered and unlikely to produce valid scientific evidence, this concern may instead result in disapproval or approval with conditions.

<sup>14</sup> If an IDE has not yet received approval or approval with conditions, subsequent submissions to FDA related to the IDE are designated as "IDE amendments." There is no required timeframe within which a response to an IDE disapproval must be submitted.

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- (ii) The methods, facilities, and controls used for the manufacturing, processing, packaging, storage, and, where appropriate, installation of the device; or*
- (iii) Monitoring and review of the investigation.*

Consistent with this regulation, FDA will generally disapprove an IDE for any of the following reasons:

- The data provided are insufficient to adequately characterize the safety profile of the device such that, based on the data provided thus far, human clinical investigation is not considered reasonable. A specific safety concern may relate to the need for additional basic device evaluation (e.g., biocompatibility, mechanical durability, drug or biologic component characterization, electrical safety, software validation, etc.) or the need for more complete characterization of the device in the anticipated clinical environment (e.g., procedural risks and mitigations, expected adverse events, etc.).
- The potential risks of the proposed study are not justified. In many cases such concerns can be addressed by providing additional information related to the potential risks and/or benefits of the study, or by making changes to the proposed clinical investigation or device.
- The proposed study design or analysis plan is inadequate. This is most applicable to pivotal studies since many elements of the study design can impact the potential for the clinical investigation to support a future marketing application. Such elements include: primary safety and effectiveness endpoints, key study design assumptions, important enrollment criteria, and important study procedures and assessment methodologies.

As noted in 21 CFR 812.30(c)(1), a disapproval letter will contain a complete statement of the reasons for disapproval. If the sponsor submits an IDE application that contains major fundamental flaws that preclude approval, FDA's identified deficiencies may describe broad concerns rather than contain a comprehensive list of each of FDA's specific concerns. In addition, FDA's review may not focus on elements of the IDE that are likely to be substantially changed by the sponsor in order to address FDA's broader concerns. In such cases, FDA's complete statement of the reasons for disapproval will clearly identify the fundamental deficiencies. Once the sponsor submits an amendment to the IDE submission to address the broad concerns that have been identified, FDA can complete a substantive review of the submission. FDA may advise the sponsor that a pre-submission discussion may be helpful prior to the sponsor formally responding to the IDE disapproval. Where appropriate, sponsors should consider requesting a pre-submission meeting before submitting an IDE.

## **8 Major Considerations for IDE Applications**

FDA considers many factors when determining whether an IDE should be approved. The following section discusses several common, important factors that FDA considers, although it is not intended to be a comprehensive list.

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### **8.1 Non-clinical Testing**

FDA reviews the non-clinical test data provided to support the basic safety and performance of the device. The type and extent of non-clinical data needed depend on several factors, including: whether the device is an *in vitro* diagnostic, an implanted device, or a device external to the body; the duration of use; and the expected performance requirements. Examples of bench data that may be needed include testing to demonstrate acceptable biocompatibility, sterilization, electrical performance, mechanical performance and durability, drug or biologic characteristics for combination products, and software validation. In many cases, animal data may also be needed to demonstrate acceptable safety and/or performance in *in vivo* conditions to support initiation of a clinical investigation.

### **8.2 Category of Clinical Investigation**

The category (i.e., feasibility or pivotal) of the proposed clinical investigation may impact FDA's assessment of which elements of the IDE application are most important with regard to IDE approval. For example, compared to a pivotal study, an IDE application for a feasibility study may be supported by less nonclinical data, as long as the existing data meet the standard for IDE approval. See 21 CFR 812.30. Additional nonclinical data may be generated as development proceeds, and as the manufacturer establishes device and performance parameters with greater certainty. For pivotal studies, in addition to an assessment of safety, FDA will consider whether the study is appropriately designed to support a marketing application.

### **8.3 Risk Assessment**

FDA considers whether the expected risks to study subjects are reasonable. It is important to note that this assessment considers many factors, including the severity of the medical condition, the patient population being studied, the current treatment options that are available to potential study subjects, and the evidence provided to support the potential for benefit to study subjects. FDA may be more willing to accept a higher risk profile or a lesser initial demonstration of potential benefit if the medical condition is serious and/or the available treatment options are limited.

FDA recognizes that in rare cases, clinical investigations of devices are not designed to offer the potential of benefit to study subjects. For example, a feasibility study may be proposed in which subjects are briefly tested with an investigational device (which is expected to have no lasting effect) during an otherwise clinically-indicated procedure. For those clinical investigations, the tolerance for the incremental risk of the clinical investigation is generally lower than that for studies that have the potential to offer direct benefit to subjects, and that risk should be outweighed by the expected value of the data to be gathered.

### **8.4 Study Design Elements**

The elements that FDA will consider in its review of the study design will depend on the device characteristics and risk profile, the medical condition being studied, and the goals of the clinical investigation. For feasibility studies, FDA's review will generally focus on subject safety issues, enrollment criteria, clinical methodology, and whether the information that will be gathered is appropriate to support the study goals (e.g., to support the design and

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initiation of a future pivotal study). For pivotal studies, FDA will also focus on elements of the study design that may impact the ability of the study to provide valid scientific evidence<sup>15</sup> to support a future marketing application. These elements include primary safety and effectiveness endpoints, assessment methodologies, randomization and blinding, the statistical analysis plan, case report forms, monitoring plans, and the use of external review bodies (e.g., Data Monitoring Committees, Clinical Events Committees, and core labs). These elements are critical to ensuring that the clinical investigation is likely to generate valid data at its conclusion. If a proposed pivotal study is unlikely to generate data that would support marketing clearance or approval, FDA may consider it unreasonable to expose study subjects to the risks of the device and may therefore disapprove the study.

### **8.5 Informed Consent Document**

The process of informing potential study subjects of the possible risks, benefits, and alternatives associated with participation in the clinical investigation is a necessary element of proper study conduct. FDA closely reviews the informed consent document as part of the IDE review. In order to support approval of the IDE, the informed consent document must meet the requirements of 21 CFR Part 50. Additional information on informed consent can be found on FDA's website:

(<http://www.fda.gov/RegulatoryInformation/Guidances/ucm126431.htm>).

### **8.6 Least Burdensome**

FDA is committed to fostering innovation and ensuring timely public access to safe and effective new products. FDA defines the term "least burdensome"<sup>16</sup> as a successful means of addressing a premarket issue that involves the most appropriate investment of time, effort, and resources on the part of industry and FDA. Application of the least burdensome principles to premarket requirements helps to reduce regulatory burden and save FDA and industry resources, while protecting the public health by maintaining the safety and effectiveness of medical devices.

## **9 Supplements to Approved IDEs**

Supplements to approved IDEs are submitted for several reasons, including the following:

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<sup>15</sup> 21 CFR 860.7 (c)(2): Valid scientific evidence is evidence from well-controlled investigations, partially controlled studies, studies and objective trials without matched controls, well-documented case histories conducted by qualified experts, and reports of significant human experience with a marketed device, from which it can fairly and responsibly be concluded by qualified experts that there is reasonable assurance of the safety and effectiveness of a device under its conditions of use. The evidence required may vary according to the characteristics of the device, its conditions of use, the existence and adequacy of warnings and other restrictions, and the extent of experience with its use. Isolated case reports, random experience, reports lacking sufficient details to permit scientific evaluation, and unsubstantiated opinions are not regarded as valid scientific evidence to show safety or effectiveness. Such information may be considered, however, in identifying a device the safety and effectiveness of which is questionable.

<sup>16</sup> Additional information is provided in the guidance entitled "The Least Burdensome Provisions of the FDA Modernization Act of 1997: Concept and Principles" (available at <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm085994.htm>).

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- To request approval for or to notify FDA of changes to the clinical investigation or the investigational device;<sup>17</sup>
- To provide the annual or final IDE reports to FDA;
- To report to FDA on unanticipated adverse events or other information related to the ongoing clinical investigation; or
- To request approval for Compassionate Use or to notify FDA of an Emergency Use.<sup>18</sup>

For IDE supplements that require FDA approval, the FDA decision process is similar to that described for original IDE submissions, with the same decision options (i.e., approval, approval with conditions, and disapproval) and review and response timelines. A notable difference between FDA’s review of such supplements and the review of an original IDE submission is that FDA disapproval of the supplement does not imply that the IDE study itself is disapproved. For example, if a supplement to an approved IDE requests approval for changes to the clinical investigation and that supplement is disapproved, the sponsor may not implement the requested changes. However, the original IDE clinical investigation remains approved and may continue. For IDE supplements that are notifications or reports, FDA will respond to the sponsor within 30 days if FDA has questions or requests for additional information; otherwise, FDA may close the submission without issuing a formal response to the sponsor.

## **10 Examples**

The following are generic examples of how different IDE decision mechanisms may be employed.

### **10.1 Example 1**

A sponsor submits an original IDE application to request approval to conduct a 30-subject feasibility study for a permanently implanted device to treat a serious chronic medical condition. The study is intended to provide data to support a future pivotal study.

FDA’s review results in the following conclusions:

- The data provided are sufficient to support feasibility clinical evaluation under the rigorous monitoring plan proposed.
- Because questions remain regarding the consequences of the long-term presence of the device, longer term animal data that include histology may be needed before a pivotal study exposing a large number of subjects to the device can be approved.
- The sponsor’s proposed follow-up assessments do not include a particular evaluation that is important for assessing the device’s performance.
- The informed consent document does not communicate a potential risk relevant for this study.

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<sup>17</sup> The guidance document entitled “Changes or Modifications During the Conduct of a Clinical Investigation,” (available at [www.fda.gov/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm082145.htm](http://www.fda.gov/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm082145.htm)) discusses the types of changes that require FDA approval and those that qualify for notification.

<sup>18</sup> The guidance entitled “Guidance on IDE Policies and Procedures,” (available at [www.fda.gov/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm080202.htm](http://www.fda.gov/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm080202.htm)), discusses Compassionate and Emergency Use.

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FDA determines that, while the informed consent issue must be corrected before enrolling subjects, none of the other concerns should preclude the sponsor from initiating the feasibility study. Therefore, FDA issues an approval with conditions letter to the sponsor. The letter states that the sponsor may initiate enrollment in the study, using an informed consent document that is modified to include the potential risk discussed above, on the condition that, within 45 days from the date of FDA's letter, the sponsor also modifies the follow-up visits to address FDA's concern. The letter also informs the sponsor of a future consideration related to the likely need for a longer-term animal study prior to initiation of a future pivotal study unless the sponsor is able to provide additional data or a scientifically valid rationale for why such a study is not needed.

The sponsor submits a supplement to the IDE to respond to FDA's approval with conditions letter within 45 days. The submission provides a modified clinical protocol and informed consent document which fully address the issues identified in FDA's letter. Therefore, FDA approves the IDE without conditions. In the IDE approval letter, the sponsor is reminded of the future consideration communicated in FDA's previous letter.

### **10.2 Example 2**

A sponsor submits an original IDE application to request approval for a 300 subject pivotal study to evaluate the safety and effectiveness of a permanently implanted device to treat a serious chronic medical condition.

FDA identifies the following issues that must be addressed before study initiation:

- Inadequate non-clinical durability testing to evaluate a potential mode of catastrophic failure.
- Inappropriate control group for safety and effectiveness comparisons

FDA also identifies other issues which the sponsor must address, but do not preclude initiation of the study, including:

- Minor inadequacies regarding definitions associated with the safety endpoint
- Statistical questions regarding the proposal for an interim analysis

Based on the first two concerns, FDA disapproves the study. The deficiencies provided in FDA's letter articulate each of FDA's four concerns, specifically noting which deficiencies were the basis for disapproval.

In response to FDA's letter, the sponsor submits an amendment to the IDE that includes additional test data and a modified clinical protocol. The amendment specifically responds to each deficiency that FDA identified in its letter. FDA's review of the amendment does not identify any issues that preclude the sponsor from initiating the study. FDA determines that the durability test data that were provided strongly suggest good long-term performance of the device and are sufficient to support study of the device in a small group of subjects. However, the data are not adequate to fully address the identified deficiency and longer term non-clinical durability testing should be conducted before the entire study cohort is exposed

## *Contains Nonbinding Recommendations*

### *Draft - Not for Implementation*

to the risks of the study. FDA also identifies some minor outstanding concerns with other clarifications and modifications made in response to the deficiencies that FDA identified.

FDA issues a staged approval with conditions letter that allows the sponsor to begin enrollment in the study, for up to 50 subjects, on the condition that the sponsor addresses the issues identified in FDA's letter within 45 days. One of the outstanding issues conveyed to the sponsor is a request that the sponsor conduct longer term durability testing concurrent to enrollment in the study and that the response to FDA's approval with conditions letter include a detailed commitment to conduct this testing.

The sponsor submits a supplement to the IDE to respond to the issues identified in FDA's approval with conditions letter within 45 days. FDA determines that all of the responses are acceptable. Therefore, FDA issues a staged approval without conditions. The enrollment continues to be limited to 50 subjects while the durability testing is ongoing. A future consideration is included in the approval letter to remind the sponsor that the clinical investigation will not have a sufficient sample to support the overall study goals (e.g., support a marketing application) until the full planned cohort of subjects is studied.

Two months later, with 37 subjects enrolled in the study, the sponsor submits an IDE supplement to provide the results from the durability testing and requests approval to enroll up to 300 subjects. FDA finds the results acceptable and grants approval for the sponsor to enroll the entire study cohort.

## **11 Conclusions**

FDA recognizes the public health benefit of permitting well-designed clinical investigations of medical devices to proceed in a timely and efficient manner while ensuring proper subject protections. When determining whether to approve an IDE application, FDA considers many factors, as discussed in this document. Where appropriate, FDA seeks to offer flexibility in how outstanding issues can be addressed (i.e., approval with conditions, staged approval, and future considerations) to allow clinical investigations to commence without unnecessary delay, while ensuring that human subjects are adequately protected.