の試験に関する IDE 規則改正要望の嘆願書の検討、ODE（医療機器評価部）の初期相（臨床）試験の審査手順のレビュー及び ODE 部長の助言を経て策定された。本ガイダンスに概説された概念及び手順は、直ちに実施すべきである。

ATTACHMENT
別添

GUIDANCE ON THE REVIEW OF INVESTIGATIONAL DEVICE EXEMPTIONS (IDE) APPLICATIONS FOR FEASIBILITY STUDIES
IDE における使用可否試験の審査に関するガイダンス

INTRODUCTION
はじめに

On November 21, 1984, the American Society for Artificial Internal Organs (ASARIO) submitted a citizen petition requesting FDA to amend the investigational device exemptions (IDE) regulation to allow limited clinical investigations of significant risk devices to be subject to less than the full IDE requirements.

1984 年 11 月 21 日、米国人工内部臓器学会は、FDA に対して IDE 規則の改正を求める市民嘆願書を提出した。それは、重大なリスクを伴う機械器具に関してIDE規則の全てを適用しない限定的な臨床試験を許容することを求めていた。

FDA may not be able to accept the petition in its entirety but recognizes the importance of providing flexibility in the review of IDE applications for feasibility studies, as long as the subjects' safety and welfare are ensured.

FDA はこの嘆願書の全面的な受け入れはできないが、被験者の安全と福祉が保証される限りにおいて、IDE 申請資料の審査に弾力性を与えることの重要性は認識している。

While CDRH has been exercising its discretion in the review and approval of feasibility studies, it has become apparent that this procedure needs to be formalized in order to be consistently applied by the reviewing divisions and to advise the research clinical community of these procedures.

CDRH（医療機器・放射線保健センター）は、これまで使用可否試験の審査及び承認に対して配慮を与えてきたが、審査担当部署が一貫性をもってこのような配慮ある手続きが運用され、臨床試験を行う者に助言を与えることができるよう、手続きを公式化することが必要となった。

It is relatively easy for a sponsor to identify a feasibility study by merely pointing out that the study involves a new device or a new technology and will involve only a few human subjects.

治験依頼者にとっては、使用可否試験を特定することは、その試験が単に新しい機械器具あるいは新しい技術を用いており、しかも少数の被験者を用いることを示すにすぎず、相対的に容易なものである

It is much more difficult to establish the criteria for relief from specific requirements of IDE regulation while assuring that patients are not placed at unreasonable risk. Relief can only be granted on a case-by-case basis, and continual assessment and analysis of the review of feasibility studies is essential to developing more concise guidance.

患者が不当なリスクにさらされないことを保証しながら IDE 規則の特別な要求事項を軽減する判断基準を確立することははるかに困難なことである。軽減はケースバイケースの対応によってのみ認められ、更に簡明なガイダンスを確立するためには、使用可否試験の審査に対する継続的な評価及び分析が必要である。

This guidance document outlines principles which should be considered when reviewing IDE applications for feasibility studies. It is expected that application of these principles will facilitate the review and approval of feasibility studies, to the extent consistent with research subjects' safety and welfare and within ethical standards.

本ガイダンス文書は、使用可否試験のための IDE 申請を審査する場合に考慮すべき原則を概説するものである。これらの原則の適用は使用可否試験の審査及び承認を被験者の安全及び福祉の面での一貫性をもって倫理基準の範囲内で容易にするであろう。

THE CONCEPT OF FEASIBILITY STUDIES
使用可否試験の概念

In a developmental process, a device is designed to meet a clinical need and testing

begins in the laboratory using animal and/or bench methodology. Once the design and operating parameters have been subject to adequate preclinical tests, the developer may wish to conduct an initial limited study in humans to confirm the design and operating specifications before beginning an extensive clinical trial.

開発の過程において、機械器具はその臨床における必要性を満たすために設計され、動物を用いた試験及び／又はベンチテストが実験室で始められる。ひとたび設計及び動作パラメータが十分な非臨床試験に供されると、開発者は機械器具の設計及び動作の仕様を確認する目的で人を用いた最初の限定的な試験を大規模な臨床試験の開始前に実施したいと望むことがある。

The initial study may indicate that minor or major changes in the device or its manufacture are necessary before proceeding. It may also indicate that the device does not meet expectations and it will be terminated. The performance of the device in the limited study serves to establish the parameters for the larger clinical study, such as sample size and indices of measurement.

最初の臨床試験は、機械器具自体又はその製造に関する軽微又は重要な変更が次相に進む前に必要となる可能性を示唆している。またそれは、当該機械器具が期待に沿わない場合は試験が中止される可能性も示唆している。限定された臨床試験における機械器具の性能は、より大規模な臨床試験のパラメータすなわちサンプルサイズ及び評価項目等の整備に役立つ。

Inherent in the utility of the limited study is the importance of maintaining sufficient flexibility for the researcher to make adjustments in the device, its manufacture or the investigational plan in the early stages of clinical testing without the need for repeated prior FDA approval.

本来、限定された臨床試験の活用においては、開発初期相の臨床試験に関して反復した FDA による事前許可を要求することなく、試験実施者が機械器具、製造方法もしくは試験計画に調整を加えることに対する十分な弾力性を維持することが重要である。

REVIEWER GUIDANCE
審査ガイダンス

1. APPLICABILITY
1．適用

This guidance applies to limited clinical investigations of significant risk medical devices which are intended to provide data on the device's feasibility for diagnostic or therapeutic clinical use. IDE applications subject to the guidance are those which are identified by the sponsor as feasibility studies and which demonstrate that they meet the general considerations applicable to such studies as note below.

本ガイダンスは、重大なリスクを伴う機械器具の臨床試験に対して限定的に適用され、その臨床試験の目的は、当該機械器具の臨床における診断又は治療の使用可否に関するデータを提供することとする。本ガイダンスに基づく IDE 申請は、臨床試験の治験依頼者によりその旨が示され、その種の試験に関して適用される下記の一般的留意事項を満足することを証明するものとする。

A feasibility study may also be identified as phase 1 studies, pilot studies, prototype studies, introductory trials or feasibility studies, or which is characterized as a feasibility study from the objectives of the investigational plan.

使用可否試験は、その試験計画に示された目的によって、第一相試験、パイロット試験、プロトタイプ試験、導入試験あるいは使用可否試験と呼ぶこともできる。

2. INTERACTIONS WITH SPONSORS
治験依頼者との相互関係

FDA encourages early and continued interactions with device innovators and potential IDE sponsor to establish a rapport which will expedite the review process. Device technology is advancing rapidly and FDA must develop and nurture lines of communication in order to anticipate problems, training needs and other resources necessary to review applications.

FDA は、審査プロセスを迅速にできるような意思疎通を確実にするために、機械器具の発明者と予定される IDE 治験依頼者との間の早期かつ継続的な相互協議を推奨する。医療機器の技術進歩は急速であり、それらの問題点、IDE 申請を審査するために必要となる訓練その他のリソースを予測するために、FDA としてはコミュニケーションルートを確保し養成しなければならない

The sponsor or researcher gains by being able to plan an acceptable preclinical and clinical approach to product development. The sponsor and reviewer should also explore possible waivers that could be granted.

製品開発は、治験依頼者もしく研究者が許容される非臨床試験及び臨床的な

アプローチの計画が可能となることによって前進する。治験依頼者及び審査官はまた、容認可能となる免除事項についても探求すべきである。

3. GENERAL CONSIDERATION FOR ORIGINAL AND SUPPLEMENTAL IDEs
初回及び変更 IDE に関する一般的留意事項

Original IDEs: IDE applications for feasibility studies will vary in scope but typically will include one investigator at one site with a limited number of subjects, usually ten or less. Data from the feasibility study will not be considered as pivotal evidence of safety and effectiveness but rather as a basis to finalize and confirm the device design and determine its potential for further development. FDA will continue to require that an IDE application for a feasibility study address all the elements of an IDE application unless a waiver is approved.

初回 IDE: 使用可否試験の IDE 申請はその適用範囲が多岐にわたるものの、単一の医療機関の一人の治験医師が通常１０名以下の限られた人数の被験者を用いることを特徴としている。使用可否試験のデータは安全性及び有効性に関する主たる臨床証拠とはみなされず、むしろ、機械器具の設計仕様の確定・確認及び以後の開発に関する見極めの根拠とされるものである。FDA は今後も使用可否試験の IDE 申請においては、免除事項が承認されない限りは IDE 申請の全ての要素を求める。

Generally, reviewers should focus their attention upon the device's potential risk to subjects. Additional concerns, e.g., a rigorous examination of the investigational plan, may be delayed until the next phase of development where the study is designed to determine the device's safety and effectiveness. The IDE regulation provides that an application may include anticipated changes to a device during the course of an investigation. For a feasibility study, FDA and the sponsor may employ this provision to qualify a range of device changes and testing parameters that can be undertaken by the sponsor without the need for further FDA approval.

一般的に審査者は、機械器具において被験者に対して可能性のあるリスクに注目すべきである。その他の懸案としては、例えば試験計画の厳格な点検が開発の次相、すなわち試験が機械器具の安全性及び有効性の判定のためにデザインされる時点にならないとできないことが挙げられる。IDE 規則では、IDE 申請には当該機械器具に予測される当該試験期間中の変更を述べてよいとしている。使用可否試験においては、FDA 及び治験依頼者は、治験依頼者が行う可能性のある機械器具及び評価項目の変更に関して FDA の追加承認を必要としない範囲

を正当化するにあたって、IDE 規則の試験中変更に関する記述を適用することができる。

Supplemental IDEs: The IDE regulation provide that changes affecting the scientific soundness or the rights, safety and welfare of subjects need to be submitted to FDA for approval prior to implementation. IRB approval is also required when the changes affect the rights, safety and welfare of subjects. FDA and sponsors should use these criteria to the maximum extent possible to limit the type of changes needed to be submitted as supplements. It is the sponsor's responsibility to determine whether a change meets the criteria. All changes, whether major or minor or whether submitted as a supplement, should be described in progress reports, end-of-study reports and in request for expansion of the investigation.

変更 IDE： IDE 規則は、科学的妥当性又は被験者の人権、安全性及び福祉に影響を及ぼす変更に関して、変更実施に先立ち FDA の承認を得るために申請することを求めている。IRB の承認もまた、被験者の人権、安全性及び福祉に影響を及ぼす変更に関して必要となる。FDA 及び治験依頼者は、変更 IDE 申請が必要となる変更を可能な限り最大限限定するために、上記の判断基準を用いるべきである。それらの変更が上記の判断基準に該当するか否かの判定責任は治験依頼者にある。また、全ての変更についてそれらが重大であるか軽微であるか、また変更 IDE として提出されるか否かに係わらず、進捗報告書、試験終了報告書及び試験拡大要望書の中で記載すべきである。

4. SPECIFIC IDE REQUIREMENTS AND CONSIDERATIONS
IDE 個別要求事項及び留意点

An IDE application for a feasibility study must address all the elements required by the IDE regulation unless a waiver is granted for a specific element. Elements that are not relevant may be indicated as "not applicable." Summary information, in lieu of full reports, is acceptable provided that the summary is sufficiently detailed and comprehensive to permit knowledgeable evaluation of the data.

使用可否試験の IDE 申請は、免除が許可された事項を除き IDE 規則で要求された全ての事項を含まねばならない。該当しない事項については、「非適用」と記載すること。報告書の代わりに要約を用いる場合、その内容がデータの見識ある評価ができる程度に十分包括的であり、かつ、詳細であれば差し支えない。

Preclinical Studies: It is the sponsor's, responsibility to define and conduct adequate

tests to establish the lack of unreasonable risk and the expected performance of a device prior to clinical use. A limited trial may represent the initial introduction of a device into a human population, therefore, FDA must be assured that a sufficient battery of tests have been completed. It is the prerogative of the sponsor to indicate whether some preclinical tests (e.g., chronic toxicity) are not essential to early clinical studies and will be initiated only if the device will undergo further clinical study.

非臨床試験： 機械器具の臨床使用に先立ち、その不当なリスク除去及び期待する性能を証明するために十分な試験を特定し実施することは、治験依頼者の責任である。限定された臨床試験は機械器具の患者への使用の初期導入を意味するため、FDA は十分な試験が終了していることを確認しなければならない。治験依頼者は、ある種の非臨床試験（例えば慢性毒性）は早期の臨床試験において必須ではなく、次の段階の臨床試験に移行する際に開始する方針を提示することの優先権を有する。

Investigational Plan: The sponsor must include a thorough risk analysis which describes the risks to the subject, how they will be minimized and a justification that they are reasonable in relation to the expected benefits. The scope and duration of limited studies will vary, but in general, are less ambitious than full clinical studies which provide the pivotal evidence of safety and effectiveness. The investigational plan should have a valid scientific objective and reasonable study protocol. Disapprovals should be limited to situations where there are critical safety-related concerns. Other deficiencies can be corrected or clarified under a conditional approval decision.

臨床試験計画： 治験依頼者は、被験者に対するリスク及びそれらを最小限にする方策とともに、リスクが期待される利益と比較して妥当であることを正当化する内容を述べた綿密なリスク分析（文書）を含めなければならない。限定された臨床試験の範囲及び期間は多様であるが、一般的には、安全性及び有効性の主要な証拠を提供するフルスペックの臨床試験よりは簡便なものとなる。臨床試験計画には、科学的に通用する試験目的及び妥当な試験プロトコールを記載すべきである。不承認は、安全性に係わる重大な問題点が存在する場合に限るべきである。その他の不足点に関しては、条件付き承認によって修正又は明確化ができる。

Manufacturing and Control Data: In some developmental programs which lead to feasibility studies, FDA recognizes that traditional manufacturing information may not exist. As noted above, often devices do not proceed to further development if the early

studies do not prove satisfactory and so only pilot manufacturing processes may be used. It is incumbent upon the sponsor to establish a reasonable process of design, manufacture, quality control and testing and to indicate to FDA in an IDE application where other standard procedures are unnecessary or premature. FDA should tailor its deficiencies to the circumstances that exist and the stage of development. Expanded clinical studies that may follow early studies may require additional assurances regarding manufacture and quality control as the numbers of devices to be distributed increase. The conditional approval decision should be employed as much as possible.
製造・品質管理データ： FDA は、伝統的な製造方法に関する情報が使用可否試験に結びつく開発段階においては存在しないことを認識している。上述のごとく、早期の試験が満足な結果をもたらさなかった場合、その機械器具が次の開発相に移行せず、パイロット製造の工程のみが用いられる場合がある。設計、製造、品質管理及び試験検査の妥当なプロセスを策定し、IDE 申請資料として FDA に提示することは、その他の SOP が不要もしくは未完成であったにせよ、治験依頼者の責務である。FDA はこれらの不足点について、背景状況及び開発段階を勘案して処理すべきである。早期の臨床試験に引き続き行われる可能性のある拡大された臨床試験においては、出荷される機械器具の数量が増加することから、製造・品質管理に関して更なる保証が必要となる場合がある。それ故、可能な限り条件付き承認とすべきである。

Informed Consent: Attention should be paid to the informed consent's description of the nature of the study, i.e., explanation of the purpose of the research, and indication that the subject is one of the first exposed to the device.
インフォームドコンセント： 同意説明文書の記述に関しては、試験の性質、例えば研究目的の説明、及び被験者は当該機械器具が用いられる最初の患者群の一人あることの明示に注意を払うべきである。

Other IDE Application Requirements: All other aspects of IDE application for feasibility studies, including investigator agreement, IRB information, sales information, environmental impact statements and labeling should be evaluated under a conditional approval decision unless there are extenuating circumstances.
その他 IDE 申請に必要な事項： 使用可否試験の IDE 申請におけるその他の事項としては、特に情状酌量を必要とする状況でない限り、治験医師との合意書、IRB 情報、販売情報、環境に対する影響に関する陳述書及び（機械器具の）表示を含むべきであり、条件付き承認のもとで評価されるべきである。

ANALYSIS OF FEASIBILITY STUDIES
使用可否試験の分析

ODE will conduct an analysis of the types of IDE applications being submitted for feasibility studies. The purpose of this analysis is to determine whether the guidance is providing sufficient direction to reviewers and flexibility to researchers. It will also further establish the nature and extent of feasibility studies.

ODE（医療機器評価部）は、使用可否試験として提出されたIDE申請の種類を分析する。この分析の目的は、本ガイダンスが審査官にとって十分な指針を与えているか、また、研究者にとって弾力性を提供しているかを見極めることにある。この分析はまた、使用可否試験の性質及び範囲に関する更なる明確化をもたらす。

The IDE Staff will collect the following information in their analysis:

- device type;
- objectives of the study;
- study design;
- number of investigators and sites;
- study sample size;
- duration of study;
- conclusions of the study;
- use of the data;
- percent of device types progressing to expanded trials;
- time to approval of studies and percent of approvals;
- percent of applications accepted without additional information; and
- waivers granted.

IDE担当職員は、分析に際して下記の情報を収集する。

- 機械器具の種類
- 試験の目的
- 試験のデザイン
- 試験実施医療機関数
- 被験者数
- 試験実施期間
- 試験の結論
- データの利用

- 次相治験拡大への進展率
- 試験実施の承認までの期間及び承認%
- 追加情報なしに承認となった%；及び
- 許可された免除事項

SUMMARY
要約

The reviewer should remain cognizant of the following principles when examining IDE applications for feasibility studies:
審査官は、使用可否試験の IDE 申請を審査するにあたって下記の原則を認識すべきである。

- o Focus the review on the risk/benefit ratio and place less emphasis on the scientific thoroughness
- 審査は個々の綿密性に対してよりむしろリスク対利益のバランスに重点を置くこと

- o Open and maintain lines of communication with researchers and sponsors to forestall problems
- 問題を未然に防ぐため、研究者及び治験依頼者とのコミュニケーションルートを確保・維持すること

- o Employ maximum flexibility, where appropriate
- 可能であれば最大限の弾力性を持たせること

- o Use conditional approval decisions to the fullest extent when deficiencies exist
- 不足がある場合にあっても、最大限条件付き承認とすること

- o Consult with the Program Operation Staff (POS) on application of the guidance when necessary
- 本ガイダンスの適用に関しては、必要に応じてプログラム運営スタッフ（POS）に相談すること

Changes or Modifications During the Conduct of a Clinical Investigation; Final Guidance for Industry and CDRH Staff

Document issued on: May 29, 2001

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

Investigational Device Exemptions Staff
Program Operations Staff
Office of Device Evaluation

Preface

Public Comment

Comments and suggestions may be submitted at any time for agency consideration to Dockets Management Branch, Division of Management Systems and Policy, Office of Human Resources and Management Services, Food and Drug Administration, 5630 Fishers Lane, Room 1061, (HFA-305), Rockville, MD, 20852. When submitting comments, please refer to the exact title of this guidance document. Comments may not be acted upon by the agency until the document is next revised or updated.

For questions regarding the use or interpretation of this guidance contact Sheila Brown at 240-276-4034
.

Additional Copies

Additional copies are available from the Internet at:
http://www.fda.gov/cdrh/ode/guidance/1337.pdf, or CDRH Facts-On-Demand. In order to receive this document via your fax machine, call the CDRH Facts-On-Demand system at 800-899-0381 or 301-827-0111 from a touch-tone telephone. Press 1 to enter the system. At the second voice prompt, press 1 to order a document. Enter the document number 1337 followed by the pound sign (#). Follow the remaining voice prompts to complete your request.

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Attachments

Changes or Modifications During the Conduct of a Clinical Investigation; Final Guidance for Industry and CDRH Staff

This document is intended to provide guidance. It represents the Agency's current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind the Food and Drug Administration (FDA) or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute and regulations.

I. PURPOSE

This document provides guidance on the implementation of section 201(a) of the Food and Drug Administration Modernization Act of 1997 (FDAMA) (Pub. L. 105-115), which amended the Federal Food, Drug and Cosmetic Act (the act) by adding section 520(g)(6). This new section of the act establishes criteria that allow sponsors to make certain modifications to the investigational device, including manufacturing changes, and/or to the clinical protocol during the course of the clinical investigation without prior FDA approval.

FDAMA provided for several tools to reduce regulatory burden in bringing new devices to market. Several of these provisions were specifically aimed at the clinical trial process. These include the Agreement/Determination meetings provisions and the least burdensome provisions (sections 201 and 205 of FDAMA, respectively). In addition, new section 520(g)(6) of the act, by permitting sponsors to implement certain changes during the clinical trial without prior approval, may be considered part of Congress' intent to reduce regulatory burden. Thus, this guidance document is part of the Center's effort to implement the least burdensome approach in device regulation.

As a result of this new provision, the investigational device exemptions (IDE) regulation (21 CFR 812) was amended. The amendment to the IDE regulation was published in the Federal Register as a proposed rule on July 15, 1998 and as a final rule on November 23, 1998. The preamble to the proposed IDE Modification rule included a detailed discussion of the types of changes that the agency believes are eligible for implementation under this provision as well as the kind of credible information that should be used to support the device and protocol changes. In addition, a discussion of the types of changes for which FDA believes prior approval should be obtained versus those that only require submission in an IDE annual report was also presented.

Although industry has used this new regulatory provision to a certain extent and its use is increasing, it has not been as widely utilized as had been anticipated. Additionally, both industry and CDRH staff have expressed interest in having guidance on the preparation and review of IDE submissions under this regulation. By capturing the discussion provided in the preambles to the

proposed and final rules in a guidance document, the agency hopes to encourage IDE sponsors to take advantage of this important new provision.

II. BACKGROUND

Experience has shown that during the course of a clinical investigation, the sponsor of a study will want or need to make modifications to the investigational plan, including the device and/or clinical protocol. These changes may be simple modifications, such as clarifying the instructions for use, or they may be significant changes, such as modifications to the study design or the device materials. Previously, § 812.35(a) *Changes in investigational plan* of the IDE regulation stated, in part:

> A sponsor shall: (1) Submit to FDA a supplemental application if the sponsor or an investigator proposes a change in the investigational plan that may affect its scientific soundness or the rights, safety, or welfare of subjects, and (2) obtain FDA approval under § 812.30(a) of any such change, and IRB approval when the change involves the rights, safety, or welfare of subjects (see §§ 56.110 and 56.111), before implementation.

According to § 812.25 *Investigational Plan*, the investigational plan includes the purpose of the study, the clinical protocol, a risk analysis, a description of the investigational device, monitoring procedures, labeling, informed consent materials, and institutional review board (IRB) information. Although written guidance on the types of modifications that could have been made without prior FDA approval had not previously been developed, the agency had traditionally permitted changes to all parts of the investigational plan. Thus, the device, the protocol, the monitoring procedures, labeling, etc. could be modified without approval of an IDE supplement if the changes did not affect the scientific soundness of the study or the rights, safety, or welfare of the subjects. According to this past policy, such changes were made by the IDE sponsor and reported in the upcoming annual report.

New section 520(g)(6) of the act, however, required FDA to modify the IDE regulation to explicitly permit certain changes to the investigational device (including manufacturing changes) and to the clinical protocol during the course of the clinical investigation without agency approval of an IDE supplement. Under the new law, the following changes are specifically permitted:

> (i) developmental changes in the device (including manufacturing changes) that do not constitute a significant change in design or in the basic principle of operation and that are made in response to information gathered during the course of an investigation; and
>
> (ii) changes or modifications to clinical protocols that do not affect—
>
> (I) the validity of data or information resulting from the completion of an approved protocol, or the relationship of likely patient risk to benefit relied upon to approve a protocol;

(II) the scientific soundness of an investigational plan; or

(III) the rights, safety, or welfare of the human subjects involved in the investigation.

The new law allows these changes to be made if:

(i) the sponsor of the investigation determines, on the basis of credible information (as defined by the agency) that the applicable conditions described above are met; and

(ii) the sponsor submits to the agency, not later than 5 days after making the change or modification, a notice of the change or modification.

Thus, under the new statute, sponsors may modify their investigational device, manufacturing process, and clinical protocol without waiting for agency approval if certain criteria are met. Section 520(g)(6) of the act broadens the criteria beyond that contained in the previous IDE regulation. For device and manufacturing changes, sponsors must ensure that the change does not constitute a significant change in design or principles of operation and that the change is made in response to information gathered during the course of an investigation. For protocol changes, in addition to the previous regulatory requirement that the change not affect the scientific soundness of the study or the rights, safety, or welfare of the subjects, sponsors must now also consider the impact that the change will have on the validity of the data and the risk to benefit relationship. In order for the IDE regulation to reflect the new statutory language and, as required by the new law, FDA modified the IDE regulation. New § 812.35(a) states, in part:

§ 812.35 Supplemental applications. (a) *Changes in investigational plan.*
(1) *Changes requiring prior approval.* Except as described in paragraphs (a)(2) through (a)(4) of this section, a sponsor must obtain approval of a supplemental application under § 812.30(a), and IRB approval when appropriate (see §§ 56.110 and 56.111of this chapter), prior to implementing a change to an investigational plan.
(2) *Changes effected for emergency use.*[1] The requirements of paragraph (a)(1) of this section regarding FDA approval of a supplement do not apply in the case of a deviation from the investigational plan to protect the life or physical well-being of a subject in an emergency. Such deviation shall be reported to FDA within 5 working days after the sponsor learns of it (see § 812.150(a)(4)).
(3) *Changes effected with notice to FDA within 5 days.* A sponsor may make certain changes without prior approval of a supplemental application under paragraph (a)(1) of this section if

[1] § 812.35(a)(2) has not been modified. This guidance document does not address deviations from the investigational plan to protect the life or physical well-being of a subject in an emergency (812.35(a)(2)). Such deviations are addressed in the guidance document entitled, "Guidance for the Emergency Use of Unapproved Medical Devices" (50 FR 42866, October 22, 1985) as well as in the guidance entitled, "IDE Policies and Procedures." (Issued on January 20, 1998; www.fda.gov/cdrh/ode/idepolcy.html).

the sponsor determines that these changes meet the criteria described in paragraphs (a)(3)(i) and (a)(3)(ii) of this section, on the basis of credible information defined in paragraph (a)(3)(iii) of this section, and the sponsor provides notice to FDA within 5 working days of making these changes.

(i) *Developmental changes.* The requirements in paragraph (a)(1) of this section regarding FDA approval of a supplement do not apply to developmental changes in the device (including manufacturing changes) that do not constitute a significant change in design or in the basic principles of operation and that are made in response to information gathered during the course of an investigation.

(ii) *Changes to clinical protocol.* The requirements in paragraph (a)(1) of this section regarding FDA approval of a supplement do not apply to changes to clinical protocols that do not affect: (A) The validity of the data or information resulting from the completion of the approved protocol, or the relationship of likely patient risk to benefit relied upon to approve the original protocol; (B) The scientific soundness of the investigational plan; or (C) The rights, safety, or welfare of the human subjects involved in the investigation.

(4) *Changes submitted in annual report.* The requirements of paragraph (a)(1) of this section do not apply to minor changes to the purpose of the study, risk analysis, monitoring procedures, labeling, informed consent materials, and IRB information that do not affect: (i) The validity of the data or information resulting from the completion of the approved protocol, or the relationship of likely patient risk to benefit relied upon to approve the protocol; (ii) The scientific soundness of the investigational plan; or (iii) The rights, safety, or welfare of the human subjects involved in the investigation. Such changes shall be reported in the annual progress report for the IDE, under § 812.150(b)(5).

As seen above and as presented in Attachment 1, new § 812.35(a) requires prior FDA approval for changes to the investigational device, including manufacturing changes, that constitute a significant change in design or basic principles of operation, or are not made in response to information gathered during the course of an investigation. Additionally, changes to the protocol that affect the validity of the results from the study, the risk to benefit relationship, the scientific soundness of the investigational plan, or the rights, safety or welfare of the subjects also require prior approval. On the other hand, changes to the investigational device (including manufacturing changes) and changes to the clinical protocol can be made without prior approval if the changes do not fall into any of the above categories and the IDE sponsor reports the modifications to the agency within 5 days of implementation. (Hereafter, this type of submission will be referred to as a "5-day notice.") Finally, under the new regulation, the agency codified its current policy of allowing minor changes to the investigational plan to be made via notification in the sponsor's annual report to the IDE. FDA is providing this guidance to restate the information contained in the preambles of the proposed and final rules to help clarify those types of changes that require prior approval versus those that can be reported in a 5-day notice or in the annual progress report. In addition, guidance is provided on the preparation and review procedures for industry and FDA staff, respectively, for each of these types of submissions.

III. CHANGES REQUIRING PRIOR APPROVAL VS. CHANGES SUBJECT TO 5-DAY NOTICE

Although the new statute and its implementing regulation identify certain criteria that must be satisfied in order for a change to be effected without prior agency approval, these criteria are fairly general. That is, device/manufacturing and protocol changes that could meet the criteria range from the very minor to the more complex. For example, device modifications could range from a packaging change to a change in material. Similarly, protocol changes may involve changes to the follow-up schedule for subjects or may involve the use of new primary/secondary endpoints. § 812.35(a)(3)(iii) of the regulation describes the types of credible information that sponsors should use to determine which changes could be implemented without prior approval from those that require prior approval. To assist sponsors in deciding if a change may be considered under a 5-day notice, potential changes to the device/manufacturing process and the protocol, as well as the supporting credible information for these changes, are discussed below.

A. CHANGES TO THE DEVICE OR THE MANUFACTURING PROCESS

Under the new law, certain developmental changes to the investigational device, including manufacturing changes, are eligible for implementation during the course of the clinical investigation without prior FDA approval. Modifications that constitute a significant change in design or basic principles of operation, or that were not made in response to information gathered during the course of an investigation, however, may not be made without prior approval of an IDE supplement. In the guidance document entitled, "Deciding When to Submit a 510(k) for a Change to an Existing Device,"[2] the agency identified generic types of device and manufacturing modifications. Although this guidance applies to modifications of marketed devices, the types of changes identified are also applicable to investigational devices. These include changes to the control mechanism, principle of operation, energy type, environmental specifications, performance specifications, ergonomics of patient-user interface, dimensional specifications, software or firmware, packaging or expiration dating, sterilization, and the manufacturing process (including the manufacturing site).

In the preamble of proposed IDE Modification regulation, FDA stated that all changes to the basic principles of operation of a device would be considered significant changes and solicited comments on this premise. No comments were received. Therefore, in the final rule, FDA stated that all changes to the basic principles of operation of a device should be submitted in an IDE supplement for prior approval.

For the remaining types of device and manufacturing changes listed above, the changes can range from minor to significant, depending upon the particular device, the type of modification, and the extent of the modification. According to the statute, it is the sponsor's responsibility to determine if a change made to the device or the manufacturing process would be considered a significant change requiring prior agency approval. To

[2] This guidance may be found at http://www.fda.gov/cdrh/ode/510kmod.html.

help sponsors determine if a change represents a significant change, the decision tree in Attachment 2 may be used in the decision-making process. According to the decision tree, the sponsor should first conduct a risk analysis to help identify the potential risks that the change to the device and/or manufacturing process may present. If the risk analysis identifies a new type of risk, then prior approval would be needed. If, however, no new type of risk is identified, the change may be eligible for implementation under a 5-day notice, but the sponsor should confirm this through the use of credible information.

Following the flowchart, FDA recommends that the sponsor use the data generated by design control procedures or other credible information to help determine whether the change has a significant affect on the device design. Credible information that may be used to support developmental changes in the device (including manufacturing changes) is defined in the regulation under § 812.35(a)(3)(iii)(A). Credible information may include data generated under the design control procedures of § 820.30, pre-clinical/animal testing, peer reviewed published literature, or other reliable information gathered during a trial or marketing. Any of these types of information may be used to support a design and/or manufacturing change, meeting the criteria discussed above, in a 5-day notice.

To help illustrate this decision-making process, consider a change in material from polyvinylchloride (PVC) to silicone in a central venous catheter. In accordance with the decision tree, the sponsor would conduct the risk analysis. The risk analysis would assess the impact of this change on the safety and effectiveness of the device. The analysis may determine that this change may impact the device's strength, flexibility and biocompatibility compared to the unmodified device, but not lead to the identification of any new risks. The sponsor would then proceed to evaluate the above risks using credible information. This may include conducting appropriate bench and animal testing to determine that the change does not significantly alter the device's strength, flexibility or biocompatibility. As a part of these activities, the sponsor should also conduct any other testing that may have been identified to the sponsor in an FDA-issued guidance document, disapproval letter, or conditional approval letter for this device and that is relevant to the change. If the results of the testing demonstrate that all of the risks (those identified in the risk analysis and those identified by the agency in its previous correspondence to the firm) have been adequately addressed, then the change could be implemented without prior FDA approval.

Using the same device in a second example, consider a change in the diameter of the lumen of the catheter. If no new types of risks are identified in the risk analysis, the manufacturer could proceed to conduct the verification and validation testing, as appropriate. If the testing demonstrates that the design input requirements are met, the change could be implemented without prior FDA approval. If, however, during the testing, it is determined that the intended flow rate was compromised by the change in diameter, then the manufacturer would have two options. The manufacturer could adjust the modification so that the original intended flow rate is still achieved or the

manufacturer could submit an IDE supplement, including a justification for the change, and pursue FDA approval of the modified device.

By using the data generated by design control procedures or other credible information, the manufacturer should be able to identify significant changes to the investigational device or manufacturing process. It should be noted that in the preamble to the final rule, the agency stated that changes intended to enhance significantly the safety or effectiveness of the device may be implemented without prior approval, if the developmental changes do not constitute a significant change in device design. Thus, although significant changes in design are not permitted under this new provision, changes that could have a significant effect on safety or effectiveness are permitted as long as they do not represent significant design changes. Below are some examples of device design/manufacturing changes that have been implemented through the 5-day notice provision:

A modification to the delivery system for a stent to reduce the shaft outer diameter so it could be used in a smaller sized catheter sheath introducer and therefore permit a smaller vascular access site.

A design modification to the tip of the catheter used during stent placement to reduce the risk of the tip being snagged on the stent strut when it is being withdrawn.

A change in an adhesive was implemented for an invasive device.

For a pacemaker, a change was made to the programmed mode that the device was shipped in to the mode that is most commonly used by the clinical investigators.

A marker band was added to an investigational device to enhance visualization during fluoroscopy.

The shelf life of a device was extended from 6 months to two years.

B. CHANGES TO THE CLINICAL PROTOCOL

Changes or modifications to the clinical protocol may be reported in a 5-day notice if the changes do not affect: a) the validity of the data or information resulting from the completion of the approved protocol, or the relationship of likely patient risk to benefit relied upon to approve the protocol; b) the scientific soundness of the investigational plan; or c) the rights, safety, or welfare of the human subjects involved in the investigation. The sponsor is responsible for initially determining if the change meets the statutory criteria. This determination should be made by the person in the company responsible for such decisions, and should be based on the agency's definition of credible information. Under § 812.35(a)(3)(iii)(B), credible information is defined as the