51 pages

[4110-03]

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Food and Drug Administration

[21 CFR Parts 16, 20, and 312]

[Docket No. 76N-0324]

MEDICAL DEVICES

Procedures for Investigational Device Exemptions

AGENCY: Food and Drug Administration.

ACTION: Tentative final regulation.

SUMMARY: This tentative final regulation sets forth requirements for the conduct of investigations of medical devices involving human subjects, including procedures for the submission of applications for an investigational device exemption (IDE), a description of the responsibilities of sponsors of investigations, and requirements for obtaining informed consent from human subjects. This action is taken because the Medical Device Amendments of 1976 require the Food and Drug Administration (FDA) to prescribe by regulation procedures and conditions under which medical devices intended for human use might be exempted from certain requirements of the Federal Food, Drug, and Cosmetic Act to permit investigational studies concerning safety and effectiveness.

DATES: Comments on or before September 11, 1978; notices of appearance for the public hearing on this tentative final regulation to be filed with the Hearing Clerk on or before June 12, 1978.

Proposed effective dates: The Commissioner is proposing that the final regulation based on this tentative final regulation be effective 120 days after the date the final regulation is published in the FEDERAL REGISTER.

However, sponsors of ongoing investigational studies who wish to ensure that these studies can continue without interruption during the 30-day period for FDA review of applications should submit applications by 90 days after date of publication of the final regulation in the FEDERAL REGISTER.

ADDRESS: Comments (5 copies identified by Doc. No. 76N-0324) shall be submitted to the Hearing Clerk (HFC-20), Food and Drug Administration, Room 4-65, 5600 Fishers Lane, Rockville, Md. 20857.

FOR FURTHER INFORMATION CONTACT:

Frank Morlock, Bureau of Medical Devices (HFK-122), Food and Drug Administration, 8757 Georgia Avenue, Silver Spring, Md. 20910, 301-427-7114.

SUPPLEMENTARY INFORMATION: In the FEDERAL REGISTER of August 20, 1976 (41 FR 35282), FDA Proposed regulations on investigational device exemptions. Final regulations governing investigational studies of intraocular lenses were published in the FEDERAL REGISTER of November 11, 1977 (42 FR 58874). Based on the many comments received on the proposal, the Commissioner of Food and Drugs has revised the proposal with respect to devices other than intraocular lenses and is issuing it as a tentative final regulation with opportunity for comment and a public hearing. This action will be followed by the agency's consideration of comments on the tentative final regulation and publication of a final regulation. The tentative final regulation omits Subparts D and E of the proposal regarding the responsibilities of institutional review committees and investigators, respectively. These omitted matters will be addressed by comprehensive agency-wide regulations governing all FDA-regulated clinical investigations. Also omitted are portions of Subpart C regarding the responsibilities of sponsors that have been addressed in proposed regulations on obligations of sponsors and monitors of clinical investigations, published in the FEDERAL REGISTER of September 27, 1977 (42 FR 49611). If certain responsibilities of sponsors, investigators, and institutional review committees in the area of device investigations need to differ from, or are not addressed in, these comprehensive regulations, separate supplemental regulations concerning these special or different responsibilities will be published.

To provide interested parties an opportunity to begin clinical investigations in a way that anticipates future FDA requirements, FDA will accept applications for investigational device exemptions before the effective date of the final regulation, if the applicant complies with the requirements in this tentative final regulation. Procedures for early submission of applications for investigational device exemptions are discussed at the end of this preamble.

OPPORTUNITY FOR PUBLIC HEARING

The Food and Drug Administration will hold a public hearing on the investigational device regulations. Any interested person who files a notice of appearance may participate in the hearing in accordance with Part 15 (21 CFR Part 15). The hearing will be held approximately 90 days after the date of publication of this reproposal and will be governed by Part 15 of FDA's administrative practices and procedures regulations, which specifies the requirements for filing notices of appearance. A notice of the exact date, time, and place for the hearing will appear in a future issue of the FEDERAL REGISTER.

STATUTORY BACKGROUND

The Medical Device Amendments of 1976 (Pub. L. 94-295) (the Amendments), amending the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321 et seq.) (the act) became law on May 28, 1976. Section 520(g) (21 U.S.C. 360j(g)) authorizes the exemption of devices from otherwise applicable provisions of the act to permit devices to be shipped for investigational studies to determine their safety and effectiveness. To provide flexibility in regulatory requirements, section 520(g) of the act permits variations in the procedures and conditions governing investigational device exemptions, depending on the nature, scope, and purpose of the study. The preamble to the August 20, 1976 proposal contains a detailed description of the statute.

DECISION TO PUBLISH TENTATIVE FINAL REGULATION

The period for comment on the proposal closed on October 19, 1976. Although numerous requests for extension of the comment period were received, the Commissioner decided not to extend the comment period but did agree to consider all comments received before issuing a final regulation. Because of the heavy volume of comments and the desire to increase public participation in the development of the investigational device regulation, the Commissioner decided to issue a tentative final regulation in the FEDERAL REGISTER, to be followed by a public hearing, before issuing a final regulation. A tentative final regulation has the same legal status as a proposal or reproposal; i.e., it is not final agency action. It is an interim step sometimes used by FDA to permit additional public participation before promulgating a final regulation. (See § 10.40(f)(9) (21 CFR 10.40(f)(9)).) Unless otherwise indicated, all references in this preamble to proposals under part 812 refer to part 812 as reproposed in this tentative final regulation.

DEFERRAL OF ACTION ON SPONSOR MONITOR, INVESTIGATOR, AND INSTITUTIONAL REVIEW COMMITTEE RESPONSIBILITIES

The initial proposal under part 812 (21 CFR part 812) on investigational device exemptions contained seven subparts: Subpart A set forth general provisions and provisions of applicability; subpart B described the procedures for submission and review of applications for investigational device exemptions; subparts C, D, and E set forth the responsibilities of sponsors, institutional review committees, and investigators, respectively; subpart F stated requirements for informed con-

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sent of human subjects; and subpart H stated requirements for investigational studies that do not involve human subjects.

As discussed in the preamble to the proposal, FDA is currently making a number of efforts to improve, clarify, and strengthen its regulatory program for control of investigational articles. Included in these efforts is the development of comprehensive proposed regulations by internal FDA task forces composed of representatives of FDA bureaus. These task forces are responsible for developing and proposing to the Commissioner agency policy that is uniform to the extent practicable, given differences among products, on such matters as the responsibilities of clinical investigators, sponsors for the monitoring of clinical investigations, and institutional review committees. The task force efforts produced the proposed good laboratory practice regulations for nonclinical laboratory studies, published in the FEDERAL REGISTER of November 19, 1976 (41 FR 51206), the proposed regulations on obligations of sponsors and monitors of clinical investigations mentioned above, and the proposed regulations on obligations of clinical investigators, which will be published in the FEDERAL REGISTER in the near future. These three proposals will apply to investigations of devices.

Because the investigational device proposal, with modifications, is being issued as a tentative final regulation rather than as a final regulation, and because several of the comprehensive proposed regulations prepared by the task forces will be ready for publication at the same time as this tentative final regulation or shortly thereafter, the Commissioner has decided that this tentative final investigational device regulation should cover only those matters that will not be covered in the comprehensive regulations. The Commissioner believes that the subject matter and the regulatory requirements for the conduct of clinical investigations of drugs, devices, and biologics are sufficiently similar to warrant uniform agency-wide regulatory policy in most instances.

Accordingly, this tentative final regulation revises subparts A, B, C, and F, based on comments received on the proposal. Subpart H is published substantially unchanged. Agency action on the remainder of the proposal, i.e., subparts D, E, and portions of subpart C dealing with responsibilities of sponsors for monitoring, are not addressed in this document and will be superseded by later final agency-wide regulations. Comments received on these matters are being considered by the FDA task forces in preparing the proposed comprehensive regulations. Any such proposed comprehensive regulations will, to the extent practicable, be incorporated into proposed part 812, directly or by reference, in future FEDERAL REGISTER notices. If it is necessary to deal with unique situations concerning device investigations only, the Commissioner will publish differing or additional proposed and final regulations on these matters.

In the interim, Subparts C, D, and E of the August 20, 1976 proposal governing the responsibilities of sponsors for monitoring studies, institutional review committees, and investigators, may be used as guidelines by persons filing applications for investigational device exemptions before the effective date of regulations on these subjects.

REFERENCES TO OTHER REGULATIONS AND TERMS

Where this tentative final regulation cites Part 52 (21 CFR Part 52) or sections thereof, it is referring to the proposed regulations on obligations of sponsors and monitors of clinical investigations, published in the FEDERAL REGISTER of September 27, 1977. The term "test article" in the sponsor proposal includes any "investigational device" in this tentative final regulation. The term "clinical investigation" in the sponsor proposal includes any "investigational study" in this tentative final regulation. The term "protocol" in the sponsor proposal includes any "investigational plan" in this tentative final regulation. The term "institutional review board" in the September 27, 1977 sponsor proposal and the term "institutional review committee" in this tentative final regulation are interchangeable.

Where this tentative final regulation cites Part 58 (21 CFR Part 58), it is referring to the proposed good laboratory practice regulations for nonclinical studies, published in the FEDERAL REGISTER of November 19, 1976 and originally designated as proposed Part 3e (21 CFR Part 3e). (Subchapter A was subsequently recodified and published in the FEDERAL REGISTER of March 22, 1977 (42 FR 15553); under the new numbering system, Part 3e will become final under Part 58.)

Where this tentative final regulation cites FDA regulations on the obligations of clinical investigators, it is referring to the proposal which will be published in the FEDERAL REGISTER in the near future and which will become final under Part 54 (21 CFR Part 54). Where this tentative final regulation cites FDA regulations on standards for institutional review committees or boards, it is referring to future agency regulations on this subject that will become final as Part 56 (21 CFR Part 56) and largely codify existing requirements under 21 CFR Part 312 and 45 CFR Part 46.

COMMENTS ON PROPOSAL—GENERAL

A total of 190 separate comments was received on the August 20, 1976 proposal. Of these, many were complex and quite constructive, and addressed numerous provisions of the proposal.

Many comments were received from industry, academic sources, and private practitioners, but none were received from public interest groups representing consumers and patient interests. The Commissioner hopes that these groups will comment on this tentative final regulation and will participate in the public hearing.

To obtain additional information on matters raised in the comments and to increase participation by members of the research community, FDA initiated contacts with several institutional review committees, scientists at the National Institutes of Health, the National Commission for the Protection of Human Subjects in Biomedical and Behavioral Research, and representatives of independent researchers. Memoranda of these meetings are available for review at the office of the Hearing Clerk, Food and Drug Administration.

GENERAL PROVISIONS

SCOPE

Numerous comments were received on § 812.1 (21 CFR 812.1) of the August 20, 1976, proposal. Many expressed concern that the objective of encouraging discovery and development of devices was subordinated to the objective of protecting the public health to such a degree that development of new devices would be effectively stifled. One comment suggested adding an objective of maintaining optimum scientific freedom for investigators. The Commissioner believes that changes made in the other sections of this tentative final regulation in response to comments preserve in proper balance the goal of encouraging the discovery and development of useful devices and the goal of protecting the rights of human subjects. Thus, no change was made in the statement of the scope of the regulation as originally proposed.

Because the Commissioner believes that sponsors will always request an exemption from all provisions of the act, he has deleted language in § 812.1(c)(2) of the August 20, 1976 proposal which stated that the device will not be exempted unless the sponsor requests the exemption specifically. The device will now be exempt from the requirements of the act enumerated in proposed § 812.1(c) unless the Commissioner indicates that the device is not exempt from specific provisions of the act in his order of approval or disapproval under proposed § 812.30 (21 CFR 812.30).

APPLICABILITY

Proposed § 812.2(a)(1) (21 CFR 812.2(a)(1)) provides that the regula-

subparts D, E, and portions of subpart C dealing with responsibilities of sponsors for monitoring, are not addressed in this document and will be superseded by later final agency-wide regulations. Comments received on these matters are being considered by the FDA task forces in preparing the proposed comprehensive regulations. Any such proposed comprehensive regulations will, to the extent practicable, be incorporated into proposed part 812, directly or by reference, in future FEDERAL REGISTER notices. If it is necessary to deal with unique situations concerning device investigations only, the Commissioner will publish differing or additional proposed and final regulations on these matters.

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APPLICABILITY

Proposed § 812.2(a)(1) (21 CFR 812.2(a)(1)) provides that the regula-

tions are applicable to any investigational device when used in an investigational study involving human subjects to determine whether the device is safe or effective (unless the device is excluded by the provisions of § 812.2 (b) or (d)). Proposed § 812.2(a)(2) provides that the regulations apply to any investigational study if the purpose of the investigational study is to develop data for premarket approval under section 515 of the act (21 U.S.C. 360e), to conduct research that involves a human subject or to aid in the diagnosis or treatment of any human subject.

Proposed § 812.2(b) describes studies and devices that are not subject to investigational controls by these regulations. Although certain devices may be excluded from the controls applicable to investigational devices, they may be subject to other statutory or regulatory requirements. For example, they may be subject to a premarket approval requirement, or may be required to be manufactured in accordance with good manufacturing practice regulations, or tested in accordance with good laboratory practice regulations during preclinical testing.

Proposed § 812.2(b)(1) provides that the regulation does not apply to a device used in an experiment, if it is used in a manner and for a purpose included in its labeling (where the labeling is prescribed under the act or approved under the premarket approval provisions of the act).

Proposed § 812.2(b)(2) provides that proposed Part 812 does not apply to test marketing of a device where the only "test" involved is that of determining consumer preference on matters not related to device safety or effectiveness. This provision was added in response to comments that, as originally proposed, § 812.2 would include test marketing. The Commissioner cautions, however, that when consumer preference testing is coupled with testing designed to test the safety and effectiveness of the device, that portion of the study that relates to safety and effectiveness is subject to regulation under proposed § 812.2(a)(1).

Proposed § 812.2(b)(3) provides that Part 812 does not apply to modifications of devices that are made for purposes other than testing their safety and effectiveness. FDA received an oral inquiry asking whether an investigational device exemption will be required when a qualified anesthesiologist modifies a commercially available anesthesiolgy device, in the hospital, to meet the special needs of patients or to ensure the device's proper functioning. For example, the anesthesiologist may need to substitute a smaller breathing circuit for pediatric use, or to lengthen or shorten the device's tubing for convenience depending on the configuration of the operating room. The Commissioner recognizes that some such modifications may not meet all the requirements for exemption from Part 812 under the custom device provisions in proposed § 812.2(d); for example, the anesthesiology device as modified may be used by a number of physicians or for a number of patients. Under proposed § 812.2(b)(3), however, no investigational device exemption is required for an anesthesiologist to adjust an anesthesiology device in the hospital to ensure proper functioning under the particular circumstances of use, where the adjustment does not involve a test of the safety or effectiveness of the adjusted device.

Proposed § 812.2(b)(4) provides that Part 812 does not apply to a simple joining of devices together to form a new device unless the purpose of joining the devices is to investigate the safety and effectiveness of the resulting device. An example of such a joining of devices would be attaching a computer to an electrocardiogram for the rapid comparison of charts. The same results could be obtained by using each device separately. The devices would be joined as a matter of convenience rather than to test a new operation.

Proposed § 812.2(b)(5) exempts certain diagnostic devices from Part 812. The earlier proposal contained no such exemption but invited comments on the issue. The Commissioner received numerous comments objecting to provisions that would apply investigational requirements to in vitro diagnostic products when such products are not used for diagnostic purposes (or, if used for diagnosis, are used in parallel with an approved diagnostic product).

Where use of the in vitro diagnostic product does not involve taking an extra sample but involves merely a surplus sample remaining from a previously obtained one, the risk that concerned the Commissioner, as expressed in the proposal, was that larger than normal samples might be taken for the purpose of obtaining surplus materials with which to conduct experiments. Several comments argued that although taking extra samples is an unusual procedure, it is often good medical practice to take a large enough sample to provide a surplus, to avoid additional invasive procedures should additional testing be necessary. If no additional tests must be performed, the remainder is "surplus."

The Commissioner believes that in vitro diagnostic products employing surplus samples should not be subject to regulation under this proposal, except in those cases where samples are taken for experimental purposes, or where the procedure of taking a sample presents a substantial risk to subjects, or where an in vitro diagnostic product is used in diagnosis without the parallel use of an approved diagnostic product to verify the diagnosis. Accordingly, in vitro diagnostic products are excluded from regulation under Part 812 by proposed § 812.2(b)(5) when they are not invasive, do not introduce energy into the subject, and are not used in the diagnosis of the subject without confirmation by use of a similar approved diagnostic product or procedure of established effectiveness. (However, such devices continue to be subject to applicable requirements under the regulations on labeling of in vitro diagnostic products, 21 CFR 809.10(c).) A device is not "invasive" in the context of proposed § 812.2(b)(5) if the procedure used to obtain the sample does not penetrate or pierce the skin or mucous membranes of the body (or the urethra) or the mouth beyond the pharynx, or the anal canal beyond the rectum, or the vagina beyond the cervical os.

Proposed § 812.2(b)(6) provides that Part 812 does not apply to devices intended for veterinary use. However, animal testing of devices intended for human use must comply with proposed Subpart H and proposed Part 58, the agency's proposed good laboratory practice regulations mentioned above.

Several proposals were submitted for restructuring the applicability of the regulation based on the risk presented by the investigational use of the device. While the Commissioner was unable to adopt any one of the proposals in its entirety, he agrees that applicability of the regulation should reflect the risk presented in a specific study. Accordingly, proposed Subpart B has been extensively revised to provide differing regulatory control depending on the nature of the device, (i.e., vital or nonvital investigational devices as defined in § 812.3 (q) and (r) (21 CFR 812.3 (q) and (r)), respectively) and on the degree of risk presented by the device to subjects participating in the study (i.e. substantial risk or low risk as defined in proposed § 812.3 (n) and (o) respectively).

Proposed § 812.2(c) (1) and (2) describe the applicability of the regulations to vital investigational devices and nonvital investigational devices.

All the requirements of Part 812 apply to vital investigational devices when such devices are used in studies presenting a substantial risk to subjects involved in the study. One of these requirements is that an application for an investigational device exemption be submitted to FDA under § 812.21 (21 CFR 812.21). When vital investigational devices are used in studies presenting low risk, the sponsor is required to submit to FDA only a notification under § 812.20 (21 CFR 812.20), rather than a full application

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under § 812.21. Upon receipt of the notification, FDA will inform the sponsor of the date it was received; 30 days after receipt, the sponsor may commence the study unless FDA has disapproved it. If FDA waives the 30-day waiting period, the sponsor may begin the study in accordance with the terms of the waiver.

For nonvital investigational devices used in investigational studies, submission of a notification to FDA under § 812.20(a) is required, but not a full application under § 812.21. Only when a nonvital investigational device is used in a study presenting a substantial risk to subjects must the sponsor wait 30 days after the date FDA received the notification before commencing the study.

Several comments argued that devices classified as class I or class II are of necessity inherently low risk and should be exempt from IDE regulations. (The act requires all medical devices to be classified into one of three regulatory categories: class I, general controls; class II, performance standards; and class III, premarket approval.)

The Commissioner believes that certain devices, regardless of their statutory classification, may present risk to subjects because of the manner in which they are used in studies. In other instances a class III device may present little or no risk to subjects in a properly designed study with limited goals. Because the inherent nature of the device cannot be ignored in determining risk, a definition of "vital investigational device" has been added in proposed § 812.3(q) and includes (1) those devices that are intended to support or sustain life or are for surgical implantation, or are diagnostic devices (including in vitro diagnostic products) that provide data that might reasonably be regarded as life supporting or vital to the care of the subject; and (2) those devices whose failure could result in permanent injury to the subject.

The vital investigational device category is broader than the class III statutory category and may include investigational versions of class II or even class I devices. Although the classification of devices similar to the investigational device may be considered, the principal factor in determining whether a device is vital or a study presents "risk" is the possible consequences, for subjects, of its use.

The distinction between vital investigational devices and nonvital investigational devices and the distinction between substantial risk and low risk provides a means to avoid overregulation. They also permit the applicability of these regulations to be structured in a way that avoids reliance on the statutory classification of a device and focuses on the risk to the subject. This approach renders inapplicable the discussion in the originally proposed § 812.2(b) and the accompanying preamble or applicability of these regulations to devices subject to premarket approval and the discussion in the originally proposed § 812.2(c) of applicability of these regulations to devices not currently subject to a premarket approval requirement.

Under proposed § 812.20, the sponsor is responsible for an initial determination of whether a device is vital and of the degree of risk presented to subjects in the study; the sponsor's submissions to FDA are to be based on these initial determinations. The sponsor's assessment is subject to review and modification by an institutional review committee and by FDA.

The Commissioner believes that information contained in the notification required by proposed § 812.20 or the application required by proposed § 812.21 will provide sufficient information that errors in the sponsor's assessment of whether the device is vital and of the degree of risk will be corrected either by the institutional review committee participating in the review of the study or by FDA. The Commissioner agrees with comments that it is unreasonable to require a full submission for every study regardless of the degree of risk, and he has provided an abbreviated notification procedure. However, sufficient information must be supplied to the Commissioner in the notification to enable him to review and evaluate determinations of the sponsor and institutional review committee or require further data where necessary.

Proposed § 812.2(d) exempts certain custom devices from the investigational device regulations. This change responds to comments on the proposal, which had provided that custom devices would not be exempt from the regulations. The criteria for an exemption from the regulation are based in part on section 520(b) of the act, which exempts certain custom devices from performance standards issued under section 514 and premarket approval requirements imposed under section 515, but not from investigational device regulations (ref. 2, at 45). Under § 812.2(d)(1), a device is exempt from the investigational device regulations if it necessarily deviates from generally available devices to comply with the order of a health professional designated in § 812.2(d)(2); the device is not generally available in finished form for purchase or for dispensing upon prescription; the device is not offered through labeling or advertising for commercial distribution; the device is intended either for use by an individual patient named in the health professional's order and is to be made in a specific form for that patient, or to meet the special needs of the health professional in the course of the health professional's practice; and the device is not generally available to or generally used by other such health professionals. In addition to complying with these requirements based on section 520(b) of the act, the device must be made of safe and suitable materials if it is an implant, the device cannot be intended for use in an investigational study for the purpose of determining whether it is safe or effective, and the device cannot have been the subject of an administrative determination by the Commissioner that the device is subject to Part 812. These additional controls are authorized under section 520(g) of the act as requirements necessary for the protection of the public and under section 701(a) of the act as a regulation for the efficient enforcement of the act.

The proposed custom device exemption in 21 CFR 52.15(b)(2) of the proposed regulations on obligations of sponsors and monitors, published in the FEDERAL REGISTER of September 27, 1977, will be revised to conform to the custom device exemption promulgated in the final regulation resulting from this proposal.

Proposed § 812.2(d)(2) designates the health professionals authorized to use custom devices in accordance with the regulation: physicians and dentists. Other specially qualified persons may be authorized to use custom devices by future regulations published in the FEDERAL REGISTER after opportunity for an oral hearing before the Commissioner under 21 CFR Part 15, i.e., a public legislative type of hearing.

The term "custom device" has been subject to varying usages within FDA, among its advisory committee members, and among interested health professionals and manufacturers. Similarly, there have been varying interpretations both of the statutory exemption of custom devices from standards and premarket approval requirements and of the effect of the proposed investigational device regulations on practices of manufacturers and practitioners to supply devices that meet unique individual needs.

Accordingly, the Commissioner is providing in proposed § 812.2(d)(3) several examples of situations in which devices that may be regarded as custom products would, or would not, be subject to the investigational device regulations. These examples should reduce misunderstanding of the custom device exemption, promote compliance with the investigational device regulations where no exemption is provided, and address valid concerns of commenters that it is inappropriate to subject all custom devices to investigational device controls.

DEFINITIONS

The Commissioner received numerous comments on the definitions con-

gational devices and nonvital investigational devices and the distinction between substantial risk and low risk provides a means to avoid overregulation. They also permit the applicability of these regulations to be structured in a way that avoids reliance on the statutory classification of a device and focuses on the risk to the subject. This approach renders inapplicable the discussion in the originally proposed § 812.2(b) and the accompanying preamble or applicability of these regulations to devices subject to premarket approval and the discussion in the originally proposed § 812.2(c) of applicability of these regulations to devices not currently subject to a premarket approval requirement.

Under proposed § 812.20, the sponsor is responsible for an initial determination of whether a device is vital and of the degree of risk presented to subjects in the study; the sponsor's submissions to FDA are to be based on these initial determinations. The sponsor's assessment is subject to review and modification by an institutional review committee and by FDA.

The Commissioner believes that information contained in the notification required by proposed § 812.20 or the application required by proposed § 812.21 will provide sufficient information that errors in the sponsor's assessment of whether the device is vital and of the degree of risk will be corrected either by the institutional review committee participating in the review of the study or by FDA. The Commissioner agrees with comments that it is unreasonable to require a full submission for every study regardless of the degree of risk, and he has provided an abbreviated notification procedure. However, sufficient information must be supplied to the Commissioner in the notification to enable him to review and evaluate determinations of the sponsor and institutional review committee or require further data where necessary.

Proposed § 812.2(d) exempts certain custom devices from the investigational device regulations. This change responds to comments on the proposal, which had provided that custom devices would not be exempt from the regulations. The criteria for an exemption from the regulation are based in part on section 520(b) of the act, which exempts certain custom devices from performance standards issued under section 514 and premarket approval requirements imposed under section 515, but not from investigational device regulations (ref. 2, at 45). Under § 812.2(d)(1), a device is exempt from the investigational device regulations if it necessarily deviates from generally available devices to comply with the order of a health professional designated in § 812.2(d)(2); the device is not generally available in finished form for purchase or for dispensing upon prescription; the device is not offered through labeling or advertising for commercial distribution; the device is intended either for use by an individual patient named in the health professional's order and is to be made in a specific form for that patient, or to meet the special needs of the health professional in the course of the health professional's practice; and the device is not generally available to or generally used by other such health professionals. In addition to complying with these requirements based on section 520(b) of the act, the device must be made of safe and suitable materials if it is an implant, the device cannot be intended for use in an investigational study for the purpose of determining whether it is safe or effective, and the device cannot have been the subject of an administrative determination by the Commissioner that the device is subject to Part 812. These additional controls are authorized under section 520(g) of the act as requirements necessary for the protection of the public and under section 701(a) of the act as a regulation for the efficient enforcement of the act.

The proposed custom device exemption in 21 CFR 52.15(b)(2) of the proposed regulations on obligations of sponsors and monitors, published in the FEDERAL REGISTER of September 27, 1977, will be revised to conform to the custom device exemption promulgated in the final regulation resulting from this proposal.

Proposed § 812.2(d)(2) designates the health professionals authorized to use custom devices in accordance with the regulation: physicians and dentists. Other specially qualified persons may be authorized to use custom devices by future regulations published in the FEDERAL REGISTER after opportunity for an oral hearing before the Commissioner under 21 CFR Part 15, i.e., a public legislative type of hearing.

The term "custom device" has been subject to varying usages within FDA, among its advisory committee members, and among interested health professionals and manufacturers. Similarly, there have been varying interpretations both of the statutory exemption of custom devices from standards and premarket approval requirements and of the effect of the proposed investigational device regulations on practices of manufacturers and practitioners to supply devices that meet unique individual needs.

Accordingly, the Commissioner is providing in proposed § 812.2(d)(3) several examples of situations in which devices that may be regarded as custom products would, or would not, be subject to the investigational device regulations. These examples should reduce misunderstanding of the custom device exemption, promote compliance with the investigational device regulations where no exemption is provided, and address valid concerns of commenters that it is inappropriate to subject all custom devices to investigational device controls.

DEFINITIONS

The Commissioner received numerous comments on the definitions con-

tained in the originally proposed § 812.3. Many comments objected that the proposed definitions lacked clarity, were circular, or did not provide information necessary to an applicant to understand the proposed regulation. Many proposed definitions were submitted that would have changed the effect of the applicability section (proposed § 812.2) in various ways. The Commissioner has revised many of the definitions appearing in § 812.3, added new definitions to accord with the changes made in proposed § 812.2 relating to applicability, and arranged them in alphabetical order (except that the definition of "nonvital device" follows the definition of "vital device" and the definition of "low risk" follows the definition of "substantial risk").

Several comments requested a better definition of "investigational device." Although the Commissioner believes that there will always be doubts in particular cases, the best guideline to follow is that a device is investigational when used in a study for determining whether the device is safe or effective for a particular use. Thus, a modified device that is being tested to determine the effectiveness or safety of the modification would be an investigational device. Because the definition of investigational device focuses strictly on the manner in which the device is being used, i.e., whether it is being tested for safety and effectiveness (including use of a device whose safety and effectiveness have not been established), the Commissioner has concluded that any distinction between "old" and "new" devices does not describe when the investigational device regulations would apply.

The Commissioner believes that the new definition of "investigational device" resolves most of the problems identified by the comments.

Additionally, some comments recommended that the definition of "medical device" be restricted to devices intended for therapeutic or diagnostic use involving living human subjects, as a means of removing in vitro diagnostic products from the scope of the regulation. The Commissioner notes that the term "device" is defined by statute (section 201(h) of the act) and thus cannot be amended administratively. He believes, however, that exclusion of most in vitro diagnostic products from coverage under § 812.2(b)(5) is responsive to these comments.

Proposed § 812.3(f) (21 CFR 812.3(f)) revises the definition of "investigational plan", which means a plan or protocol for using an investigational device in an investigational study, where the plan or protocol meets the requirements of proposed § 812.25 (21 CFR 812.25). Comments objected that the proposed regulations reversed the sense in which the terms "investigational plan" and "investigational study" are used in industry. Although the comments suggested that the terms be revised to reflect industry terminology, the Commissioner believes that such revision would be more confusing than the regulation as originally proposed.

Proposed § 812.3(g) revises the definition of "investigational study" to mean a study involving human subjects that is for the purpose of determining whether a device is safe or effective.

The Commissioner recognizes that the manufacturer of an old class III device may wish to gather information on clinical experience with the device for future submission to FDA after expiration of the grace period in section 501(f)(2)(B) of the act (21 U.S.C. 351(f)(2)(B)) or other purposes. (An old class III device is a device that either was in commercial distribution before the enactment of the Amendments, or is substantially equivalent to a device that was in commercial distribution before the Amendments, and that is placed in the premarket approval category, class III, by an FDA regulation under section 513(d) of the act (21 U.S.C. 360c(d)).) The Commissioner does not consider it an investigational study when the manufacturer of an old class III device distributes the device lawfully and requests some or all users to provide information on clinical experience with the device as used in its usual manner for "old" uses (commercial uses of the device, or of a substantially equivalent device, that predate the Amendments).

Proposed § 812.3(h) defines "investigator" as an individual who actually conducts an investigational study, i.e., under whose immediate direction the device is administered or dispensed to or used involving a subject. A corporation can never be an investigator. An investigator may be assisted in an investigation by other qualified investigators under his or her supervision, provided such individuals are identified as investigators in the application or notification submitted in accordance with Subpart B to obtain an investigational device exemption.

Proposed § 812.3(i) defines the term "monitor" to mean, when used as a noun, an individual selected by a sponsor or contract research organization to oversee the progress of a clinical investigation. Such a person may be a full-time employee of the sponsor or contract research organization or a consultant. When used as a verb, "monitor" means the act or reviewing the progress of a clinical investigation.

The definition of "sponsor" found in proposed § 812.3(k) is revised to eliminate the concept of financial support as a characteristic of the sponsor relationship. This change was made in response to comments that government agencies sponsoring research by means of grants would not in all instances wish to become sponsors within the meaning of the proposed regulation. Accordingly, language in the original proposal, which made a person who supported a study by financial or other resources a sponsor, was eliminated, and language was added to provide that a sponsor is any person who initiates an investigation but does not actually conduct the investigation. This change of language does not change the requirement that someone must assume the responsibilities of a sponsor in an application. However, the Commissioner is not requiring any particular person to assume these responsibilities. Thus, a government agency that supports an investigational device study by means of a grant, or a private foundation that funds such a study, would not necessarily be a sponsor unless it identified itself as such by submitting the notification or application for an investigational device exemption. However, the recipient of the grant or someone else must assume the responsibilities of a sponsor and submit an application for an exemption or notification.

The definitions of "investigator", "sponsor", and "sponsor-investigator" were modified to conform to definitions that will appear in other agency documents, e.g., "investigator" and "sponsor-investigator" are defined to refer only to a living individual. The definition of "sponsor" contemplates that the employees of a corporate sponsor may be considered investigators, not sponsor-investigators, when they undertake clinical investigations for the sponsor.

One comment noted that the term "institution" should not include a manufacturer because the manufacturer might be required to institute an in-house institutional review committee. The Commissioner believes that it is inappropriate to remove the term "manufacturer" from the definition in proposed § 812.3(b). However, he points out that a manufacturer of a device need not have an in-house institutional review committee unless a study using the manufacturer's employees as the subjects is being conducted.

Another comment suggested that "human subject" be redefined so that a human user of a device would not be a subject unless the investigational device placed the user at risk. Proposed § 812.3(m) does not change the definition of "subject." The Commissioner believes that introducing the concept of risk into the definition of "subject" would provide an opportunity to evade the regulation. The essence of being a subject is that the individual, whether healthy, sick, or at risk, is used in research.

A definition of "institutional review committee" appears in proposed

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device placed the user at risk. Proposed § 812.3(m) does not change the definition of "subject." The Commissioner believes that introducing the concept of risk into the definition of "subject" would provide an opportunity to evade the regulation. The essence of being a subject is that the individual, whether healthy, sick, or at risk, is used in research.

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§ 812.3(d). An institutional review committee is any board or committee or other formally organized group appointed for the purpose of reviewing, in accordance with current professional standards, clinical investigations or other research involving humans as subjects. Protection of human subjects is accomplished by reviewing, approving, suspending, or terminating an investigation when necessary for the protection of human subjects. By "current professional standards," the Commissioner means the standards in effect in the medical profession at any given time, and would include the Helsinki Convention, the American Medical Association standards, Department of Health, Education, and Welfare regulations and guidelines, and such other standards as may emerge over time, either nationally or locally. The term is not intended to freeze professional standards. As professional standards change, it is expected that standards applied by the committee will reflect changes in medical community ethics. The committee also must provide human protection in accordance with the requirements of Part 812. Finally, an institutional review committee is synonymous with an institutional review board.

Proposed § 812.3(q) adds a definition of "vital investigational device" as a medical device intended to support or sustain life or intended for surgical implant into the body or as a diagnostic device (including any in vitro diagnostic product) used to provide data that might reasonable be considered life-supporting or vital to the care of the subject, or as a device whose failure could result in permanent injury to the user.

Several aspects of this definition are significant. First, specifically included are certain in vitro diagnostic products and other diagnostic devices that provide information that could be vital to patient care or are life-supporting in nature. Thus, the definition specifically covers devices that provide significant diagnostic information about a patient which, if misleading or inaccurate, could result in significant misdiagnosis of the patient or incorrect therapeutic care of the patient.

Second, the definition of "vital investigational device" is similar to the definition of "critical device" in the proposed good manufacturing practice (GMP) regulations for the manufacture, packing, storage, and installation of medical devices, published in the FEDERAL REGISTER of March 1, 1977 (42 FR 11998). However, the classes of products subject to the definition will vary. Also, the definition of "critical device" in the proposed GMP regulations makes no explicit reference to in vitro diagnostic products, but would include these products because they are within the definition of "device" in section 201(h) of the act. Nonetheless, because the commissioneer believes that investigational controls might be construed as not applying to certain in vitro diagnostic products and other diagnostic devices unless specific language were added including such devices, appropriate language has been added to proposed § 812.3(q). However, a number of in vitro products are exempt from the investigational controls, but will be considered critical devices for GMP purposes. Applying GMP's but not investigational controls to certain devices is consistent because, if manufactured properly, certain devices may present no substantial risk of being either unsafe or ineffective when used in investigational studies. The Commissioner has omitted language in the definition of "critical device" found in the GMP proposal which provides that a critical device is a device declared by the Commissioner to be a critical device after consultation with the Device Good Manufacturing Practice Advisory Committee. This language is omitted because it is inappropriate in these regulations. As with the GMP regulations, the Commissioner is considering publishing a list of devices that FDA regards as vital investigational devices.

Third, the mere fact that a device is vital does not result in an automatic assignment of a particular risk category, although it is treated differently from a nonvital investigational device.

"Nonvital investigational device" is defined in § 812.3(r) as all those devices that are not vital devices; in short, all other devices. By dividing devices into these two general categories, it is possible to apply the regulatory controls in such a manner as to minimize the regulation of those devices that are nonvital and present low risk.

Several comments suggested limiting the scope of the regulations to studies that place subjects "at risk." Suggestions were made that FDA use the definition of "at risk" found in 45 CFR 46.103, Department of Health, Education, and Welfare Guidelines, Protection of Human Subjects. The Commissioner believes that the broad definition contained in 45 CFR 46.103 of the term "at risk" would not be helpful in restructuring the proposed regulation because the breadth of the definition of "at risk" would subject practically every investigational study to full investigational controls. The Commissioner believes that definitions of "risk" in this proposed regulation must differentiate between low and substantial risk situations. Accordingly, the Commissioner has added a definition of "substantial risk"; in proposed § 812.3(n) as a risk that may result in death or may produce morbidity (including disfigurement, permanent injury, or interference with the capacity to continue employment); require operation or reoperation or extension of hospitalization beyond that expected for the condition being treated, or cause rehospitalization or increased invalidism; or, at the least, produce moderate personal discomfort and the need for extensive outpatient medical care. This definition identifies a range of risks from moderate to high that may threaten subjects. If, as a possible consequence of the study, any of the conditions set forth in the definition could occur, the study must be categorized as substantial risk. On the other hand, where none of the conditions set forth in the definition of substantial risk are likely foreseeable consequences of the study, the study will fall into the low risk category explained below.

The Commissioner received a comment from the National Institutes of Health that the probability of the risk actually occurring should be considered in the definition of "risk." He has not included this factor in the definition of risk because he believes that for many studies data are simply lacking on which to base such a judgment. The Commissioner agrees that where probability data are available, the likelihood of an event's occurrence may be a basis for assigning it to a higher or lower risk category, e.g., a risk may be evaluated in terms of whether it is certain, frequent, infrequent, or rare; and such a determination may enter into the determination of whether to treat the risk presented by the study as substantial or low. The assessment of risk is designed in part to determine how much information must be submitted to FDA (e.g., a notification or an application) as well as for the purpose of determining whether the study should be initiated or continued. The definitions of "substantial risk" and "low risk" look to the likely foreseeable consequences of a study, including the additional risk to which the subject may be exposed because of the use of the investigational device. The definition of "low risk" in proposed § 812.3(o) provides that any risk other than a substantial risk is a low risk, including a situation in which there is no risk of injury to the subject or to his or her rights.

In proposed § 812.3(p), "transitional period" is redefined in response to comments to apply only to those devices (1) which either were on the market prior to May 28, 1976 or are judged by FDA to be substantially equivalent to a device marketed prior to that date, and (2) which are classified in the class III category. The transitional period is defined as extending from May 28, 1976 to either (1) 30 calendar months after the device is classified as a class III device, or (2) 90 days after a regulation requiring the submission of a premarket approval application is promulgated, whichever occurs later.

FEDERAL REGISTER of March 1, 1977 (42 FR 11998). However, the classes of products subject to the definition will vary. Also, the definition of "critical device" in the proposed GMP regulations makes no explicit reference to in vitro diagnostic products, but would include these products because they are within the definition of "device" in must differentiate between low and substantial risk situations. Accordingly, the Commissioner has added a definition of "substantial risk"; in proposed § 812.3(n) as a risk that may result in death or may produce morbidity (including disfigurement, permanent injury, or interference with the capacity to continue employment); to that date, and (2) which are classified in the class III category. The transitional period is defined as extending from May 28, 1976 to either (1) 30 calendar months after the device is classified as a class III device, or (2) 90 days after a regulation requiring the submission of a premarket approval application is promulgated, whichever occurs later.

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The Commissioner received one comment suggesting that the term "substantially equivalent" as it is used in § 812.3(p) be defined. The Commissioner believes, however, that the term cannot be better described at this time. A determination that a device is substantially equivalent is judgmental, and while reasons may appropriately be given for any particular decision so classifying a device, the terminology itself cannot be better defined except with synonyms which will provide little, if any, additional clarification. Accordingly, no definition is offered for this term. The Commissioner believes it may be possible to define the term at a later date as experience develops in determining substantial equivalency. The term is evolving into a term of art. The preambles to the proposed and final Device Establishment and Premarket Notification regulation published in the FEDERAL REGISTER of September 3, 1976 (41 FR 37458) and August 23, 1977 (42 FR 42520), contain useful guidance in interpreting this phrase.

GENERAL QUALIFICATIONS FOR AN EXEMPTION

Proposed § 812.5 (21 CFR 812.5) received only one significant comment, which stated that the proposed labeling requirements conflict with those in 21 CFR 809.10(c) for investigational in vitro diagnostic products. The Commissioner agrees and has changed the originally proposed § 812.5 to provide the option of using one of the statements prescribed in § 809.10(c) rather than the statement prescribed in § 812.5. The Commissioner notes that most in vitro diagnostic products are to be exempted from Part 812, so only some such products will have to comply with Part 812 as well as Part 809.

Proposed § 812.5(b) now includes provisions, formerly in § 812.47(a), that the labeling of an investigational device shall not represent that the safety and effectiveness of the device has been established for the purposes under investigation and shall describe relevant hazards, contraindications, adverse effects, interfering substances or devices, and precautions.

WAIVER

Proposed § 812.10 (21 CFR 812.10) elicited comments suggesting that the Commissioner be required to act on a petition for waiver in the same 30-day period in which he is required to act on the application for exemption. One comment argued that the petition for waiver should be incorporated into the application for investigational device exemption thereby requiring the Commissioner to respond within 30 days.

The Commissioner believes that by restructuring the applicability of the proposed regulation in terms of risk, and excluding from the applicability of the proposed regulation many in vitro diagnostic products and custom devices, he has reduced the need for waiver petitions. The Commissioner does not intend to delay action on a petition for waiver. However, he does not believe that in extending this privilege of requesting a waiver, which is not required by statute, he must be governed by the same 30-day response period prescribed for action on an application for an investigational device exemption. Such a time limitation in which to respond to waiver petitions may not be realistic if waiver is requested for many requirements or a major category of testing, because the evaluation of the petition may require extended discussion and review. The Commissioner assures all interested parties that petitions for waiver will be acted upon as soon as practicable, within 30 days in many cases, and that there is no intent to delay action on a petition for a waiver any longer than is necessary to evaluate it.

Another comment was that by fulfilling requirements imposed by other government agencies under a grant or contract, the petitioner should receive an automatic waiver of investigational device requirements.

The Commissioner believes that although fulfillment of requirements imposed by another agency would certainly be a major factor in determining whether to grant a petition for waiver of certain requirements, FDA's decision depends on whether the requirements imposed by the other agency sufficiently protect the public health and safety to permit the granting of the petition for waiver. The Commissioner notes that it is not the practice to waive compliance for investigational drug requirements even though a study is conducted under a grant from another government agency.

Two additional significant comments were received on proposed § 812.10. One suggested the compilation of a list of exempt products to reduce requests for waiver. The Commissioner believes that it is impossible at this time to exempt products in advance from the requirements of the proposed regulation because a product, regardless of the degree of risk associated with it in its approved use, may when used in an investigational study generate far higher degrees of risk. Additionally, the differences between individual products within a class are so great that the compilation of a list of exempt products is not feasible at this time.

A final comment suggested that any final regulation should make clear that confidential information contained in a petition for waiver would be protected from public disclosure.

The Commissioner responds that information contained in a petition for waiver is subject to the same protection as any information contained in an application for exemption as prescribed by proposed § 812.21 (21 CFR 812.21) and is disclosable to the public upon request according to the same rules that define when information contained in an application for exemption can be disclosed, i.e., proposed § 812.38.

INFORMATION PREVIOUSLY SUBMITTED

Proposed § 812.12 (21 CFR 812.12) provides that previously submitted data may be incorporated by reference in any subsequent submission. Proposed § 812.12 received no significant comment and remains unchanged.

REQUIREMENTS APPLICABLE TO EXPORTERS OF DEVICES

Proposed § 812.19 (21 CFR 812.19) received a number of negative comments. However, one comment supported FDA's position in attempting to protect other countries from the export of devices that would not be subject to adequate controls in the country of import since such a position is necessary to further the foreign policy interests of the United States.

Comments argued that the policy enunciated in proposed § 812.19 was unwise, unlawful, and unconstitutional. One comment argued that the provision requiring the exporter to obtain the foreign government's approval is probably unconstitutional because no clause in the Constitution supports a Federal police power protecting a foreign citizen. Additionally, the United States has no power or authority to "legislate for the health of the world." Other comments noted that proposed § 812.19(b)(2) (i) and (ii) afford protection to foreign citizens beyond that intended by the legislation. These comments suggested that exporters should have to comply only with the law of the foreign government receiving the exported product. Other comments stated that the export requirements should be satisfied where there is an approved application if the country to which the device is exported is willing to accept the device. Submission by the manufacturer of proof from the importing country of willingness to permit import of the device should satisfy FDA where there exists an approved investigational device exemption.

The Commissioner received several comments suggesting that many countries lack agencies or officials charged with regulating investigational devices. The fear was expressed that it would be impossible to comply with the requirements of this section when there is no available foreign official to certify approval of the device. Further, even where such a foreign official exists, there may be no administrative apparatus within the foreign country

period in which he is required to act on the application for exemption. One comment argued that the petition for waiver should be incorporated into the application for investigational device exemption thereby requiring the Commissioner to respond within 30 days.

The Commissioner believes that by restructuring the applicability of the proposed regulation in terms of risk, so great that the compilation of a list of exempt products is not feasible at this time.

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The Commissioner responds that information contained in a petition for tries lack agencies or officials charged with regulating investigational devices. The fear was expressed that it would be impossible to comply with the requirements of this section when there is no available foreign official to certify approval of the device. Further, even where such a foreign official exists, there may be no administrative apparatus within the foreign country

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for controlling the device after import. Several comments argued that because such situation may be anticipated to exist, FDA must be satisfied with a notification from the sponsor-exporter of an intent to ship; in which case, after a stated time elapsed during which neither an approval nor denial was received from the foreign government, the exporter would be free to ship upon verifying the notification and certifying to FDA that the device complies with the law of the foreign country to which export is proposed. Other comments suggested that any limitations on exports should be confined to the health and safety of the United States.

The Commissioner believes that proposed § 812.19 closely parallels section 801(d) of the act (21 U.S.C. 381(d)) as amended and accurately reflects Congressional intent. The Commissioner believes that section 801(d) of the act is a constitutional exercise of Congress' plenary power to regulate imports and exports by prescribing the conditions under which products manufactured in the United States may be exported. Any impact that section 801(d) and the proposed regulations would have on the conduct of foreign nationals is incidental to these legitimate product export controls. The Commissioner points out that export controls apply not only to investigational devices but also to investigational new drugs. Furthermore, the application of export controls to exported investigational devices serves U.S. interests by making it less attractive for firms to try to avoid the requirements of section 520(g) of the act (21 U.S.C. 352(g)) by conducting studies of investigational devices in foreign countries lacking similar requirements; reducing the unfair advantage that would accrue to such firms; and helping to ensure that data offered to FDA in support of device premarket approval applications were developed under conditions in which human subjects were protected and that ensure the collection of valid scientific data.

The Commissioner has concluded that Congress intended for FDA to consider the effects of exportation of an investigational device on the public health and safety of the receiving country, when he makes the determination required by section 801(d)(2) of the act (21 U.S.C. 381(d)(2)), "* * * that the exportation of the device is not contrary to public health and safety and has the approval of the country to which it is intended for export." He believes that it is constitutional for Congress to require FDA to consider effects of American exports on receiving countries, as a constitutional exercise of Congress' authority to control exports. In addition, the requirement is similar to the general duty of nations under international law to refrain from causing avoidable harm to other nations. For these reasons, in administering § 812.19, the Commissioner may in some cases decide that the mere existence of an investigational device exemption for domestic studies is not sufficient by itself to warrant the export of the device unless the Commissioner is assured that there is satisfactory provision within the importing country to control the device after import. In some instances, previously exported products are later imported into the United States.

The Commissioner has revised proposed § 812.19 to parallel the statute more closely. The statute requires that before export of an unapproved device that is currently subject to a performance standard, premarket approval requirement, investigational device exemption, or banned device regulation, FDA must determine that the exportation of the device is not contrary to the public health and safety and has the foreign government's approval.

The Commissioner prefers that the importing country have sufficient regulatory controls and organizational apparatus to ensure that the device is investigated under conditions equivalent to those under which it is being investigated or could be investigated within the United States. Although the revision of proposed § 812.19 does not require the exporter of an investigational device to obtain an investigational device exemption before export in every case, the Commissioner reserves the right to refuse to permit the export of the device under section 801(d) of the act if he believes that the conditions under which the device will be tested in the importing country are such that the device would not be subject to adequate control

The Commissioner recognizes that in dealing with foreign governments, unique and unusual situations may occur, e.g., it may be difficult to determine which foreign government agency should approve importation of the device. Rather than rewrite the requirements of this regulation in terms of the unusual, the Commissioner prefers to deal with unusual situations as they are presented, on a case by case basis. If an exporter discovers that there is no foreign official who can grant clearance to the proposed import of the device, the manufacturer, or exporter, or sponsor should request a waiver. The Commissioner will respond to such situations as he deems appropriate after investigating the facts and, where necessary, in consultation with the Department of State or other Federal agencies.

The Commissioner rejects the suggested procedure for an exporter to be able to export the device after a given period of time had elapsed and to certify that he was in compliance with foreign law. The Commissioner does not believe that such a procedure complies with section 801(d) of the act.

NOTIFICATION AND APPLICATION

The Commissioner received numerous comments relating to the application form, many requesting a simplified notification procedure.

NOTIFICATION

The Commissioner agrees with comments that a simplified notification procedure is appropriate for many studies. Accordingly, proposed § 812.20 (21 CFR 812.20) has been revised to provide for an abbreviated application, called a notification, where a vital investigational device is to be used in a low risk investigational study or when a nonvital investigational device is to be used in an investigational study. The notification consists of the name and address of the sponsor, the signature of the sponsor or the sponsor's authorized representative, the name and description of the device, a summary of the investigational plan, the location(s) of the study, the sponsor's agreement to comply with FDA regulations and monitoring procedures, the institutional review committee's approval of the study and agreement to comply with FDA regulations on institutional review committees (future Part 56), a summary of the investigational study, the institutional review committee's assessment of whether the device is vital or nonvital and the risk presented by the study, and the name of the investigators and each investigator's agreement to comply with FDA regulations regarding the obligations of clinical investigators (including Subpart F and future Part 54).

The Commissioner emphasizes that the institutional review committee must specifically assess the risk to which the study exposes human subjects; and that the committee's approval, its determination whether a device is vital and its risk assessment, signed by the chairman, must be contained in, or attached to, the notification. Only if the committee assesses the risk presented by a vital investigational device to be low will the notification be accepted by FDA. The Commissioner cautions that the determination as to whether a device is vital and as to risk assessment by both the sponsor and the committee are subject to review and reversal by FDA. In the event that FDA determines that an application is needed and not a notification, the sponsor will be notified to postpone or suspend the study and submit an application containing the information required by § 812.21 (21 CFR 812.21).

Proposed § 812.20(a)(2) provides that three completed copies of the notification, together with all accompanying materials, should be sent by registered

safety and has the approval of the country to which it is intended for export." He believes that it is constitutional for Congress to require FDA to consider effects of American exports on receiving countries, as a constitutional exercise of Congress' authority to control exports. In addition, the requirement is similar to the general duty of nations under international

respond to such situations as he deems appropriate after investigating the facts and, where necessary, in consultation with the Department of State or other Federal agencies.

The Commissioner rejects the suggested procedure for an exporter to be able to export the device after a given period of time had elapsed and to certify that he was in compliance with

event that FDA determines that an application is needed and not a notification, the sponsor will be notified to postpone or suspend the study and submit an application containing the information required by § 812.21 (21 CFR 812.21).

Proposed § 812.20(a)(2) provides that three completed copies of the notification, together with all accompanying materials, should be sent by registered

mail or hand delivered to the Bureau of Medical Devices, Document Control Center (HFK-20), Food and Drug Administration, 8757 Georgia Avenue, Silver Spring, Md. 20910. The outside wrapper must be appropriately labeled "Notification of Intent to Commence Testing an Investigational Device."

A sponsor who wishes to do so may always submit an application under proposed § 812.21, even though the study may qualify for the submission of a notification.

The Commissioner believes that this provision will simplify procedures for obtaining an exemption and that it is justified by the low risk associated with the studies eligible for the proposed notification procedure.

Additionally, the procedure for filing an application or notification was revised to permit hand delivery.

APPLICATIONS FOR EXEMPTION

Formerly proposed § 812.20, dealing with the contents of an application for an investigational device exemption, is renumbered § 812.21. Proposed § 812.21(b)(1), as revised, permits a description of the important components of the device in lieu of a complete statement of the components of the device. Any anticipated changes in the components of the device must be identified in the application.

All information furnished must be in sufficient detail that a scientist or physician familiar with the general type of device, by not necessarily expert with regard to the specific device, can make a knowledgeable judgment as to the anticipated safety or effectiveness of the device in the study. This change complements the change from "complete" to "important components"; the information provided must be sufficient so that a qualified person need not be an expert with respect to the specific device to make a knowledgeable judgment regarding the safety and effectiveness of the device in the proposed study.

Similarly, proposed § 812.21(b)(3) is modified to delete the requirement of including a complete statement of methods, facilities, and controls used in the manufacture, processing, packaging, and storage of the device. The Commissioner is requiring instead a description of those methods, facilities, and controls used for the manufacture, processing, packaging, and storage in enough detail that a person informed in that general area can make a knowledgeable judgment about the anticipated safety and effectiveness of the device in the proposed study.

The requirement in formerly proposed § 812.21(b)(4) that the sponsor list those sections of the act from which exemption is sought has been deleted because it is unlikely that a sponsor will seek less than a complete exemption from all statutory requirements for which an exemption can be requested.

Proposed § 812.21(b)(4) directs the sponsor to state the location of every institutional review committee that will monitor any portion of the study and state each such committee has received a copy of the investigational plan and report or prior investigations, together with all other materials required by the committee (such as separate protocols not described in the plan). Generally, the investigator rather than the sponsor would provide this and other information to the institutional review committee and otherwise deal with the committee; the investigator would inform the sponsor of his or her actions and those of the committee.

A copy of the plan, report, and other information required by any institutional review committee must also be submitted to FDA. The Commissioner has determined that it is necessary for the protection of the public health and safety for the Commissioner to have a copy of the full investigational plan to decide whether testing should commence, even where there has been review by an institutional review committee. The Commissioner points out that a summary of the plan is, however, adequate in a notification under proposed § 812.20 (unless the Commissioner requests a copy of the full plan after receiving a notification that contains only a summary).

The Commissioner cautions that although FDA will consider an application which requests waiver of the institutional review requirement of proposed § 812.42, the application will be evaluated on a basis different from that used when an institutional review committee has approved and will review the study. The Commissioner may disapprove an otherwise adequate application if the absence of a committee to monitor the study may expose subjects to undue risks.

Proposed § 812.21(b)(5) as revised requires only the committee chairman, rather than each member of the committee, to sign a statement that the committee has reviewed and approved the plan and report of prior investigations. The Commissioner agrees with the comments that the requirement for all members of the committee to sign, taken together with the quorum requirements, could have effectively given a minority member a veto over the project.

An objection was made to the use of the term "supervise" when referring to committee functions with respect to its review of the study. The Commissioner agrees that it is more appropriate for the committee to protect human subjects by reviewing reports of unexpected adverse effects, by periodic monitoring, and by determining whether the study should be continued rather than by supervising the study.

Proposed § 812.21(b)(6) was revised in response to a comment that the sponsor should submit all forms and informational material to be given to human subjects, including all forms to be used to obtain informed consent as required by Subpart F. Copies may be appended to the investigational plan.

One comment proposed that language be added stipulating that the sole purpose of requiring submission of all informed consent forms to be used in the study is to assure compliance with the informed consent requirements in proposed §§ 812.120 and 812.130 (21 CFR 812.120 and 812.130). The comment argued that no single type of informed consent should be mandatory and that each investigator should be responsible for obtaining the consent form best suited to the investigator's needs which complies with the regulation. The comment explained that the purpose of the suggested change is to clarify that no responsibility is assumed by FDA or the sponsor for professional liability where informed consent forms must be changed to comply with the regulations.

The Commissioner is not adopting this suggestion. the original proposal did not contain inflexible provisions as to the type of informed consent required, and none are required in this revision. The Commissioner expresses no opinion on the professional liability of sponsors or investigators where changes must be made in consent forms to meet FDA requirements.

Proposed § 812.21(b)(7) requires the sponsor to submit a copy of the investigator's curriculum vitae together with the investigator's agreement (as required) to comply with regulations regarding obligations of investigators. Copies of agreements signed by each investigator participating in the study shall be submitted.

Proposed § 812.21(b)(8) provides that the sponsor must submit (1) a copy of all informational material, including labels, to be supplied to investigators under § 812.47(a); (2) a description of the scientific training and experience the sponsor considers appropriate to qualify an individual as suitable to investigate the device; (3) the sponsor's written precedures for monitoring the investigational study in compliance with 21 CFR Part 52 (the proposed regulations on obligations of sponsors and monitors of clinical investigations, published in the FEDERAL REGISTER of September 27, 1977); and (4) the name and a summary of the training and experience of the individual who is to monitor the study for the sponsor.

Proposed § 812.21(b)(9) provides that the sponsor shall state, to the best of the sponsor's knowledge, whether an

make a knowledgeable judgment about the anticipated safety and effectiveness of the device in the proposed study.

The requirement in formerly proposed § 812.21(b)(4) that the sponsor list those sections of the act from which exemption is sought has been deleted because it is unlikely that a sponsor will seek less than a complete

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with 21 CFR Part 52 (the proposed regulations on obligations of sponsors and monitors of clinical investigations, published in the FEDERAL REGISTER of September 27, 1977); and (4) the name and a summary of the training and experience of the individual who is to monitor the study for the sponsor.

Proposed § 812.21(b)(9) provides that the sponsor shall state, to the best of the sponsor's knowledge, whether an

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institutional review committee has ever disapproved or terminated any investigational study of the device and the reasons for such action.

A comment objected that this provision is irrelevant to determining whether the present application should be approved. The Commissioner believes that such information is relevant and, if not stated in the application, might give rise to further questions at a later stage in the proceeding. Should the study be suspended or terminated after it has begun because of questions relating to a previous institutional review committee disapproval, a sponsor might lose considerable investment and valuable scientific data might be lost. For this reason, the Commissioner believes that full disclosure in the application serves the best interests of all concerned. The Commissioner believes that a prior refusal by an institutional review committee to approve the study would not necessarily prejudice the present application unless the prior disapproval disclosed grounds which would justify disapproving the present study.

Proposed § 812.21(b)(10) requires the sponsor to state that the sponsor will comply with all the requirements applicable to sponsors under this chapter. This agreement includes the specific provisions of Subpart C and proposed Part 52 on the responsibilities of sponsors and monitors in clinical investigations.

Proposed § 812.21(b)(11) required the sponsor to notify FDA if the sponsor intends to charge investigators or subjects for the device.

The Commissioner believes that while it may be appropriate for sponsors in certain instances to charge for the device, the Commissioner is concerned that commercialization of the device not occur under the guise of recouping investment. Therefore, the Commissioner insists that he be notified of an intent to charge. Such notification is not to be construed as FDA approval to begin commercial distribution of the device. The Commissioner at his discretion may request additional information regarding the cost of manufacture and development in deciding whether to approve the application. However, the requirement that the sponsor justify the sponsor's decision to charge for the device has been omitted in response to comments that devices, unlike drugs, may individually be very costly to produce and that the only way a manufacturer can recoup such manufacturer's development cost is to charge for the device.

Proposed § 812.21(b)(12) requires the sponsor to state the sponsor's reasons for any request for a waiver of the requirement of § 812.30(a) that the study not begin before 30 days after FDA has received the application.

Proposed § 812.21(b)(13) permits the Commissioner at his discretion to request an environmental analysis report from the sponsor. Such a report need not be submitted on a routine basis. However, the Commissioner believes that when FDA would be required to prepare an environmental impact statement on approval of an investigational device exemption, the sponsor is in the best position to provide the information needed to prepare this statement. The Commissioner may condition his approval of the application on receipt of an accurate and adequate report. Failure to submit an adequate report, when requested, would be grounds for disapproving the application. Of course, as with other requests for information, the sponsor may refuse to provide the information and treat the request as a disapproval for purposes of requesting a regulatory hearing under Part 16 as discussed below.

Proposed § 812.21(b)(14) requires the sponsor to submit any other information relevant to the review of the application which FDA may require to be submitted. The type of information required may be obtained by making specific requests to sponsors either orally, by telephone, or in writing.

The Commissioner received comments that FDA could effectively prevent a sponsor from obtaining a hearing to review FDA administrative action simply by making repeated requests for information without ever approving or disapproving the application. The Commissioner agrees that the sponsor is entitled to request a hearing with respect to an application if FDA requests additional information.

Accordingly, proposed § 812.21(c) permits the sponsor to refuse to provide any information requested under proposed § 812.21(b)(14) and treat the application as disapproved for purposes of requesting a regulatory hearing under proposed § 812.30 to review the Commissioner's determination.

However, proposed § 812.21(c), as revised, also provides that if the Commissioner's request for information does not receive a response within the time stated in the request, the Commissioner will treat the application as withdrawn, and so notify the sponsor, to foreclose the possibility of a sponsor simply not responding to requests for information and arguing that such sponsor is still in technical compliance with the regulation because such sponsor's application is pending.

Other comments objected that the information that may be requested was not restricted to relevant information. The Commissioner agrees that only information related to the review of the application will be required to be submitted.

INVESTIGATIONAL PLAN

Proposed § 812.25 (21 CFR 812.25) states the requirements for an investigational plan.

Proposed § 812.25(a)(2) has been revised to delete the requirement that FDA be notified of all changes to be made in the plan, in response to comments that only foreseeable changes should be reported. Only anticipated or foreseeable changes need be cited in the investigational plan.

Proposed § 812.25(a)(11) requires the description of all important components of the device in the investigational plan. The Commissioner believes it would be illogical not to require a description of all important components of the device in the investigational plan while requiring them to be described in the application submitted to FDA, which the institutional review committee might not see.

Proposed § 812.25(d) has been added to prescribe the requirements or the contents of a summary of an investigational plan. Such requirements were not included in the original proposal. A summary of a plan would be required to include an adequate and accurate summary of each element of a plan under § 812.25(a).

REPORT OF PRIOR INVESTIGATIONS

Proposed § 812.27 (21 CFR 812.27) sets forth the requirements for reports of prior investigations and experience with the device that must be submitted.

Proposed § 812.27(b)(1) has been revised in response to comments that the report of prior investigations should not include complete information about preclinical investigations because the requirement may be difficult or impossible to meet if the device has a long market history. The Commissioner has revised proposed § 812.27(b)(1) so that the sponsor need only provide a bibliography of publications relevant to the study, which could be fewer in number than those relevant to the particular device, and provide copies of significant publications, both adverse and supporting. By eliminating the requirement that the bibliography submitted be complete, and by requiring instead that the publications be relevant to the clinical study, the Commissioner avoids imposing a burden of exhaustive and unnecessary research. The requirement will be satisfied if the bibliography is relevant to the investigational study proposed, thereby excluding studies not bearing on the specific test to which the device is to be subjected. Insofar as possible, all relevant material submitted should be complete.

Section 812.27(b)(2) now requires that unpublished information both adverse and supporting shall be provided (if available to the sponsor) in sufficient detail so that a scientist or physician not necessarily an expert with respect to a specific device could make a knowledgeable judgment regarding its anticipated safety and effectiveness in the proposed study.

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Proposed § 812.21(b)(14) requires the sponsor to submit any other information relevant to the review of the application which FDA may require to be submitted. The type of information required may be obtained by making specific requests to sponsors either orally, by telephone, or in writing.

The Commissioner received comments that FDA could effectively prevent a sponsor from obtaining a hearing to review FDA administrative action simply by making repeated requests for information without ever approving or disapproving the application. The Commissioner agrees that the sponsor is entitled to request a hearing with respect to an application if FDA requests additional information.

Accordingly, proposed § 812.21(c) permits the sponsor to refuse to provide any information requested under proposed § 812.21(b)(14) and treat the application as disapproved for purposes of requesting a regulatory hearing under proposed § 812.30 to review the Commissioner's determination.

However, proposed § 812.21(c), as revised, also provides that if the Commissioner's request for information does not receive a response within the time stated in the request, the Commissioner will treat the application as withdrawn, and so notify the sponsor, to foreclose the possibility of a sponsor simply not responding to requests for information and arguing that such sponsor is still in technical compliance with the regulation because such sponsor's application is pending.

Other comments objected that the information that may be requested was not restricted to relevant information. The Commissioner agrees that only information related to the review of the application will be required to be submitted.

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Section 812.27(b)(2) now requires that unpublished information both adverse and supporting shall be provided (if available to the sponsor) in sufficient detail so that a scientist or physician not necessarily an expert with respect to a specific device could make a knowledgeable judgment regarding its anticipated safety and effectiveness in the proposed study.

Proposed § 812.27(c) provides that prior investigations of a device shall not be considered adequate to justify clinical trials with human subjects unless the conditions of the prior investigations are comparable to the conditions of the proposed study.

Several comments indicated that it is unnecessary for FDA to know in every instance the place where the prior studies were conducted. The Commissioner agrees and proposed § 812.27(d)(2) limits the requirement to provide details on prior tests to information that is sufficiently detailed to permit scientific evaluation. Where scientific evaluation would necessitate identifying the qualifications of the person performing the test or including other precise information, such information must be submitted. Proposed § 812.27(d) also provides that, except where tests on laboratory animals would be unnecessary, e.g., where there have been adequate in vitro tests or clinical experience, prior investigations will be considered adequate only if there have been tests in animals and these tests show it is reasonably safe to begin clinical trials with humans.

Proposed § 812.27(e) provides that a summary of the same type of information concerning components or ingredients of a device (e.g., a bibliography and copies of other unpublished relevant information) must be provided as is required in proposed § 312.27(b) (1) and (2) when the components or ingredients may have a significant effect on the safety or effectiveness of the device and information concerning such components or ingredients is needed to justify investigational use of the device on human subjects.

FDA REVIEW OF AND ACTION ON AN APPLICATION

Section 812.30 (21 CFR 812.30) describes the procedure for FDA's review of applications for exemptions and prescribes criteria for acting on such applications.

Proposed § 812.30(b) was modified to permit the Commissioner, when rejecting a resubmitted application, to suggest that it be further revised and resubmitted, while authorizing the sponsor to treat the Commissioner's suggestion as a final disapproval for purposes of requesting a regulatory hearing for conformity with proposed § 312.21(c).

In response to comments, the criteria for disapproving applications in § 812.30(c) have been changed to give the Commissioner discretion to decide whether to disapprove an application (or notification), where grounds for disapproval exist. Thus, the words "shall disapprove" have been replaced by the words "may by order disapprove."

Proposed § 812.30(e) of the August 20th proposal contained criteria for assessing risks when disapproving an application. These criteria still apply but have been moved to proposed § 812.35(a)(11) (21 CFR 812.35(a)(11). To comply with section 520(h) of the act (21 U.S.C. 360j(h)), the Commissioner has added new § § 312.30(f) and 812.35(e) requiring FDA to make publicly available a detailed summary of information on which FDA bases a decision to approve an exemption from a banned device regulation, to disapprove an application, or to withdraw an exemption.

GROUNDS FOR WITHDRAWAL OF AN EXEMPTION

Proposed § 812.35 enumerates the grounds for withdrawal of an exemption.

The grounds are similar to the grounds contained in proposed § 812.35 (a) and (b) of the August 20th proposal.

Comments said that the provisions seem to show suspicion of the good faith of sponsors in the absence of any evidence that sponsors will not follow the rules. Accordingly, proposed § 812.35 deletes the provisions of formerly proposed § 812.20(b)(6) that the application might be disapproved merely because there is reason to believe the investigation would not be conducted in accordance with the investigational plan. However, in the event that evidence exists of actual failure to comply with the plan, grounds would exist as provided in § 812.35(a)(6) for withdrawing an exemption previously granted.

Proposed § 812.35(c) as revised provides that the Commissioner may, in his discretion, continue in effect an exemption for which there are grounds for withdrawal if the facts do not lead the Commissioner to conclude that the risks outweigh the benefits to subjects. Withdrawal will not occur mechanically. Failures to conform may be cured in some instances by submitting additional information or correcting procedures used in the study.

Proposed § 812.35(a)(11) provides that the Commissioner may withdraw an exemption if the Commissioner determines that the proposed investigational study subjects human subjects to undue risks.

Proposed § 812.35(a)(11) also provides that in assessing risks the Commissioner shall consider certain specified criteria. Formerly proposed § 812.30(e)(3) evoked comments objecting to the language "legally effective informed consent" as redundant since a consent that is not informed cannot be legally effective while a legally effective consent must be informed. The Commissioner believes that FDA should adopt the language of 45 CFR 46.103 (DHEW Guidelines, Protection of Human Subjects) since to delete this language might signal that the requirement differs in substance, which is not the case. This language was included in the DHEW Guidelines to make clear that the consent must comply with State laws to be "legally effective."

Proposed § 812.35(d) provides for reinstatement of the exemption if the sponsor satisfies the Commissioner that grounds for withdrawal no longer apply. Emphasis should be placed on the fact that the burden is on the sponsor to convince the Commissioner that the grounds for withdrawal no longer apply.

WITHDRAWAL OF AN INVESTIGATIONAL DEVICE EXEMPTION

The Commissioner received several comments suggesting a prehearing conference procedure prior to withdrawal of the exemption. The Commissioner believes that such a procedure is cumbersome and unduly restricts his power to take swift action to protect the public health. Experience with prehearing conferences relating to withdrawing IND's proved that the prehearing conference took on all the trappings of the hearing itself. The resulting delay from provision for a conference would not be in the public interest, particularly as the sponsor does have an opportunity for a hearing. However, in appropriate cases, informal meetings may be held in accordance with 21 CFR 10.65

One comment received on proposed § 812.35 suggested that, once the time period for evaluation of the application had elapsed, FDA could no longer reevaluate the data and withdraw the exemption. The same comment also suggested that approval of the report of prior investigations, once approved for purposes of this part, should be valid for support of any subsequent premarket approval application.

The Commissioner does not agree with this comment. The public health could be jeopardized if the sponsor had submitted false or misleading data in such sponsor's original application and if FDA, because it had failed to perceive the misstatement in its review of the application, was bound forever to its original determination and powerless to correct the mistake. All data submitted to FDA are subject to continual evaluation for the protection of the public health. The Commissioner would be remiss in his duty were he to allow himself to be bound by a prior mistake. A sponsor can be protected by ensuring that all data submitted to FDA are accurate.

For similar reasons, the Commissioner will not guarantee to sponsors that the report of prior investigations of a device submitted under part 812 will satisfy requirements for such a report in a premarket approval application. The Commissioner advises that the Commissioner is not now in a position

§ 812.30(c) have been changed to give the Commissioner discretion to decide whether to disapprove an application (or notification), where grounds for disapproval exist. Thus, the words "shall disapprove" have been replaced by the words "may by order disapprove."

Proposed § 812.30(e) of the August 20th proposal contained criteria for assessing risks when disapproving an application. These criteria still apply but have been moved to proposed § 812.35(a)(11) (21 CFR 812.35(a)(11). To comply with section 520(h) of the act (21 U.S.C. 360j(h)), the Commissioner has added new § § 312.30(f) and 812.35(e) requiring FDA to make publicly available a detailed summary of information on which FDA bases a decision to approve an exemption from a banned device regulation, to disapprove an application, or to withdraw an exemption.

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The grounds are similar to the grounds contained in proposed § 812.35 (a) and (b) of the August 20th proposal.

Comments said that the provisions seem to show suspicion of the good faith of sponsors in the absence of any evidence that sponsors will not follow the rules. Accordingly, proposed § 812.35 deletes the provisions of formerly proposed § 812.20(b)(6) that the application might be disapproved merely because there is reason to believe the investigation would not be conducted in accordance with the investigational plan. However, in the event that evidence exists of actual failure to comply with the plan, grounds would exist as provided in § 812.35(a)(6) for withdrawing an exemption previously granted.

Proposed § 812.35(c) as revised provides that the Commissioner may, in his discretion, continue in effect an exemption for which there are grounds for withdrawal if the facts do not lead the Commissioner to conclude that the risks outweigh the benefits to subjects. Withdrawal will not occur mechanically. Failures to conform may be cured in some instances by submitting additional information or correcting procedures used in the study.

Proposed § 812.35(a)(11) provides that the Commissioner may withdraw an exemption if the Commissioner determines that the proposed investigational study subjects human subjects to undue risks.

Proposed § 812.35(a)(11) also provides that in assessing risks the Commissioner shall consider certain specified criteria. Formerly proposed § 812.30(e)(3) evoked comments objecting to the language "legally effective informed consent" as redundant since a consent that is not informed cannot be legally effective while a legally effective consent must be informed. The Commissioner believes that FDA should adopt the language of 45 CFR 46.103 (DHEW Guidelines, Protection of Human Subjects) since to delete this language might signal that the requirement differs in substance, which is not the case. This language was included in the DHEW Guidelines to make clear that the consent must comply with State laws to be "legally effective."

Proposed § 812.35(d) provides for reinstatement of the exemption if the sponsor satisfies the Commissioner that grounds for withdrawal no longer apply. Emphasis should be placed on the fact that the burden is on the sponsor to convince the Commissioner that the grounds for withdrawal no longer apply.

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The Commissioner does not agree with this comment. The public health could be jeopardized if the sponsor had submitted false or misleading data in such sponsor's original application and if FDA, because it had failed to perceive the misstatement in its review of the application, was bound forever to its original determination and powerless to correct the mistake. All data submitted to FDA are subject to continual evaluation for the protection of the public health. The Commissioner would be remiss in his duty were he to allow himself to be bound by a prior mistake. A sponsor can be protected by ensuring that all data submitted to FDA are accurate.

For similar reasons, the Commissioner will not guarantee to sponsors that the report of prior investigations of a device submitted under part 812 will satisfy requirements for such a report in a premarket approval application. The Commissioner advises that the Commissioner is not now in a position

to know whether the reports sponsors submit under part 812 will be of adequate quality to satisfy requirements for such reports in premarket approval applications.

CONFIDENTIALITY

Proposed § 812.38 (21 CFR 812.38) prescribes the rules governing confidentiality of information contained in a notification or application for an investigational device exemption and is comparable to § 312.5 of the IND regulations.

The Commissioner has already published for comment a proposed regulation concerning FDA policy on disclosure of the existence of investigational device exemptions. This proposal was published in the FEDERAL REGISTER of March 28, 1977 (43 FR 12869), correction published in the FEDERAL REGISTER of March 31 (43 FR 13587). Under the proposal, FDA would disclose the existence of an application or notice submitted to FDA seeking permission to conduct research on, or to market, a drug or device, whether or not the application or notice had previously been publicly disclosed or acknowledged. This proposal would reverse present FDA policy. Paragraph (a) of proposed § 812.38 has been published for comment as part of the March 28, 1977, proposal as corrected and, accordingly, is not published in this tentative final regulation. Comments on the issue of disclosure of the existence of investigation device exemption should be sent by May 30, 1978, to the docket on the March 28, 1977, proposal (Docket No. 77-0248) rather than to the docket of this tentative final regulation.

The section was also changed from the original proposal to clarify that an individual is only entitled to an adverse reaction report relating to use of a device on that individual. Useful guidance concerning the interpretation of this section may be found in the preamble to the final regulations promulgating § 312.5 (21 CFR 312.5), published in the FEDERAL REGISTER of December 24, 1974 (39 FR 44602) and January 14, 1977 (42 FR 3094).

The Commissioner received a comment relating to confidentiality, urging that FDA only disclose adverse reactions to investigators directly involved, arguing that such investigators have the training and experience to make proper evaluations of such reports while patients would not be able to interpret such reports correctly and could be unnecessarily concerned about information that is not understood. The comment argued that present conditions which focus on professional liability require that confidentiality be assured to prevent misuse of documentation in a manner unfairly adverse to the investigation, the investigator, the device, and the sponsor.

The Commissioner disagrees with this comment. It is not the duty of FDA to protect sponsors or investigators from lawsuits by subjects. It is reasonable to provide subjects access to data concerning their own adverse reactions. Such disclosure enhances the automomy of the subject and provides the subject with information that permits such subject to take whatever action he or she believes is necessary in his or her own best interest. Moreover, such disclosure is required by the Freedom of Information Act and is consistent with the objectives of the Privacy Act.

Comments asked whether adverse reaction reports required under this regulation will be subject to release to the public under the Freedom of Information Act. The Commissioner advises that prior to approval of a device under section 515 of the act (21 U.S.C. 360e), reports of adverse reactions occurring during any investigational device exemption study are not available to the public except as provided in proposed § 812.38(c). Under proposed § 812.38(c), a subject is entitled to a report concerning his or her own adverse reaction regardless of whether the existence of the IDE has been publicly disclosed or acknowledged. The Commissioner further advises that adverse reaction reports concerning devices approved under section 515 of the act will be released consistent with the provisions of § 314.14(d)(4).

SUPPLEMENTAL APPLICATIONS

Proposed § 812.39 (21 CFR 812.39) describes the situations in which a supplemental application is required to update a notification submitted under proposed § 812.20 or an application submitted under proposed § 812.21 Generally speaking, proposed § 812.39 has not been significantly changed.

In response to comments, the Commissioner has revised proposed § 812.39(b) to provide that when a hazardous situation exists which necessitates the use of an investigational device, prior notification to FDA before using the device is not required.

COMMENTS RELATING TO SUBPART B WHICH REFLECT DIFFERING CONCEPTIONS OF THE ROLE OF INSTITUTIONAL REVIEW COMMITTEES

Many comments on subpart B imply a different conception of the role of the institutional review committee than that held by the Commissioner. Several comments proposed that whenever an institutional review committee participates in the review of a study, it should be unnecessary to submit the curriculum vitae of the investigator to FDA. Similarly, a comment suggested the labeling should not be submitted to FDA but rather to the institutional review committee. Another suggested that no medically trained monitor was necessary in light of monitoring by the institutional review committee. Yet another suggested that the reverse of the formerly proposed scheme found in § 812.21(b) be adopted so that only a summary of prior studies should be submitted to the institutional review committee, the full report being submitted to FDA. Comments reflecting still another view of the role of the institutional review committee argued that the committee need not indicate at the time the application is submitted whether it would review and approve the study. Other comments stated that it is unnecessary to delay approving the investigational device exemption until the committee approves it; rather the procedure should be the same as that used with the IND, which permits simultaneous submissions to the committee and FDA. Delay, it was objected, serves no useful purpose.

Other comments stated the institutional review committee alone should pass on the sufficiency of the informed consent form and that FDA should not require submission of the informed consent form with the application.

The Commissioner disagrees with these comments because the Commissioner believes they confuse the role that the act assigns the institutional review committee. The institutional review committee is intended by Congress (see section 520(g)(3)(A) of the act) to be an integral part of the review process and is intended to review both the plan and report of prior investigations before the submission of this information to FDA. But the Commissioner does not believe that the institutional review committee can lawfully or practically substitute for the regulatory functions of FDA. The Commissioner must have the opportunity to pass on the qualifications of investigators, the adequacy of the informed consent forms used, and the labeling of the device. Furthermore, as discussed in more detail below, the Commissioner believes that the institutional review committee is not a substitute for the sponsor's monitor in controlling the quality of the entire study, although the Commissioner points out that no such monitor would be required where the sponsor is a sponsor-investigator.

SPONSOR RESPONSIBILITIES

Proposed subpart C states requirements applicable to sponsors of investigational studies. It supplements the agency-wide proposed regulations on obligations of sponsors and monitors of clinical investigations under part 52 (21 CFR part 52) published in the FEDERAL REGISTER of September 27, 1977 (42 FR 49611) and on good laboratory practices under part 58 (21 CFR part 58) published as proposed part 3e in the FEDERAL REGISTER of November 19, 1976 (41 FR 51206).

about information that is not understood. The comment argued that present conditions which focus on professional liability require that confidentiality be assured to prevent misuse of documentation in a manner unfairly adverse to the investigation, the investigator, the device, and the sponsor.

The Commissioner disagrees with this comment. It is not the duty of mittee participates in the review of a study, it should be unnecessary to submit the curriculum vitae of the investigator to FDA. Similarly, a comment suggested the labeling should not be submitted to FDA but rather to the institutional review committee. Another suggested that no medically trained monitor was necessary in light of monitoring by the institutional

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Certain responsibilities of sponsors that were the subject of subpart C of the original investigational device proposal of August 20, 1976, have either been addressed in subpart B of this tentative final regulation or by proposed part 52. Other provisions of the original investigational device proposal will be replaced by future proposed FDA regulations on the obligations of clinical investigators and on standards for institutional review boards. This cross-reference chart explains these changes in proposed subpart C:

Provision	Aug. 20, 1976, proposal (sections)	Current (sections)
General	812.40	812.40
Review of an investigational study by FDA and institutional review committee.	812.42(a)–(b)	812.20, 812.21
		812.42(a)
		52.25
	812.60(a)	812.42(b)
	812.42(c)	812.20, 812.21
		812.39
		812.56
		52.29(b)(ii)[1]
Selection of investigators	812.43(a)	812.43(a)
	812.43(b)	812.43(b)
Control over the investigational device	812.45(a)	812.45
		52.29(b)(ii)
	812.45(b)	52.114
	812.45(c)	52.108
	812.45(d)	52.47
Monitoring the investigational study	812.46(a)	812.46(a)
		52.28
		52.128
	812.46(b)	52.28, 52.29
	812.46(c)	52.29(b)(ii)
	812.46(d)	812.46(b)
	812.46(e)	52.28, 52.29
	812.46(f)	812.46(c)
	812.46(g)	812.46(d)
Submitting information to investigators	812.47(a)	812.47(a)
	812.47(b)	812.46(e)
	812.47(c)	812.47(b)
	812.47(d)	(2)
Promotion and sale of an ivestigational device	812.50(a)	52.118
		812.5
		812.50(b)
	812.50(b)	52.118
		812.50 (a), (b)
	812.50(c)	812.50(c)
Reporting to FDA, maintaining records, and permitting inspection.	812.55(a)	812.55(a)
	812.55(b)	812.55(b)
		812.55(c)
	812.55(c)	812.55(d)
	812.55(d)	812.55(e)
		812.55(f)
	812.55(e)	812.55(g)
	812.55(f)	52.195
	812.55(g)	812.55(h)
	812.55(h)	812.55(i)
	812.55(i)	812.55(j)

[1] Future FDA investigator and institutional review regulations.
[2] Deleted.

GENERAL

Proposed § 812.40 states that the requirements of this subpart are applicable to sponsors of investigational studies, including sponsor-investigators, except as specifically provided otherwise in FDA regulations, e.g., in proposed § 812.2(e), which exempts sponsor-investigators from certain requirements.

REVIEW OF THE INVESTIGATIONAL STUDY BY FDA AND THE INSTITUTIONAL REVIEW COMMITTEE

Proposed § 812.42(a) (21 CFR 812.42(a)) requires the sponsor to meet applicable requirements for institutional review, submit a notification or application to FDA, and be granted FDA approval, where required, before any human subject is allowed to participate in, or is requested formally to consent to participate in, the investigational study.

Comments questioned the proposal to require the approval of an institutional review committee, when one is to be used, before submission of an application to FDA. The current investigational new drug regulations merely require an assurance that institutional review will be obtained prior to actual commencement of the investigation. The Commissioner believes it is desirable to require institutional review before submission of a notification or an application for an investigational device exemption because such review will enable FDA to rely on committees to screen out studies that would not be performed even if FDA reviewed them favorably, and to provide FDA with better information on the committees being used by sponsors and investigators under investigational device exemptions. The Commissioner will, for the same reasons, propose a similar requirement of prior institutional review for other clinical investigations regulated by FDA, including investigational new drug investigations, in future proposed regulations establishing standards for institutional review boards.

Several comments suggested that it is appropriate to ask potential subjects whether they will be available to participate in the study before undertaking the expense of applying for an investigational device exemption. The Commissioner agrees that it may be permissible for sponsors to make preliminary surveys of potential subjects to determine whether there will be an adequate number of subjects willing to participate in the study. Language that might be interpreted to prohibit such preliminary contacts has been eliminated. The Commissioner cautions, however, that an investigator or sponsor must not request a subject to give informal consent to the study until the study has been approved by the institutional review committee and FDA, where these approvals are required.

The Commissioner received comments that monitoring by the sponsor duplicates the review by the institutional review committee. The comments argued that the monitoring function should be assigned either to the committee or to the sponsor, but not to both. The Commissioner maintains that both sponsors and institutional review committees need to oversee investigational studies, and the Commissioner doubts that duplication of effort really will result since the monitoring responsibilities of the two groups differ. The primary responsibility for monitoring the investigator's conformity to the plan and ensuring the validity of data from the study rests with the sponsor, although these also are concerns of an institutional review committee; the primary responsibility of a committee is to review the

COMMITTEE

Proposed § 812.42(a) (21 CFR 812.42(a)) requires the sponsor to meet to be used, before submission of an application to FDA. The current investigational new drug regulations merely require an assurance that institutional rests with the sponsor, although these also are concerns of an institutional review committee; the primary responsibility of a committee is to review the

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study to ensure protection of human subjects. The sponsor's duty is to monitor a study continuously; the committee has only a general responsibility to review a study periodically. The committee, unlike the sponsor, offers a disinterested review of a study. Moreover, the statute requires device studies to be both monitored by sponsors and reviewed by committees.

Several comments from institutional review committees objected to the provision for the sponsor rather than the investigator to submit the investigational plan to the institutional review committee for approval. The Commissioner agrees that it is better for investigators rather than sponsors to submit investigational plans to institutional review committees. However, section 520(g)(3) of the act speaks of the sponsor submitting the plan (and report of prior investigations) to an institutional review committee. To respond to the comments and the agency's own preference that investigators deal with committees, but without departing from congressional intent, the Commissioner has revised proposed § 812.42(a) so that the sponsor's responsibility is now stated as ensuring that institutional review occurs, rather than submitting an application to a committee, which will be primarily the investigator's responsibility under future FDA regulations.

Proposed § 812.42(b) describes the circumstances in which institutional review is required under the investigational device regulations. A counterpart provision, proposed § 812.60(a), in the August 20 proposal would have required an institutional review committee to review and monitor an investigational study in any of three situations: When the investigational study involves institutionalized human subjects; when the study is conducted by an individual affiliated with an institution that assumes responsibility for the investigation, or when the study is conducted in an institution that has a committee meeting FDA standards. (References to § 812.60 in proposed Part 52 on obligations of sponsors and monitors of clinical investigations, published in the FEDERAL REGISTER of September 27, 1977 (42 FR 49611) should now be considered references to propose § 812.42(b).

The Commissioner believes that the purposes and processes of institutional review are now so widely accepted, and its value so generally recognized, that all clinical investigations should undergo such review unless circumstances clearly make it unnecessary, or infeasible, or inimical to the subject's interest. Therefore, he is proposing in § 812.42(b) and future agency-wide regulations to make review by an institutional review committee a general precondition to submission of any clinical investigation that is subject to requirements of the act for prior submission to FDA for review, and in some cases approval, before it can be commenced. He further proposes that FDA generally will not consider any clinical investigation in support of an application for a research or marketing permit (as defined in § 52.3(b) in the September 27, 1977 proposal) unless the investigation was conducted under an institutional review committee. This proposal would not mean that the results of the investigation need not be submitted to FDA. The usual rule that all data and information relevant to a particular article (a proposed or marketed product, for example) must be submitted remains in effect. Even in situations where the scientific validity of an investigational drug study is not in question, FDA may receive data but not use it in support of a decision to approve testing or commercial distribution of a drug because of ethical improprieties in the conduct of the study (21 CFR 312.20).

The Commissioner recognizes that there may be situations in which an institutional review committee requirement may be unneccesary, redundant, or contrary to the interests of a subject. The Commissioner therefore proposes § 812.42(d) to accept an application for waiver of the institutional review committee requirement upon a showing that the requirement is not necessary either for protecting the subjects involved or for ensuring the validity or reliability of the scientific data. The section provides, however, that the requirement will not waived in three situations: (1) When the investigation involves institutionalized subjects; (2) When it is conducted on the premises of, or utilizes personnel or resources of, an institution having an institutional review committee meeting FDA's standards; and (3) When the Commissioner finds that the risks to the subjects in the investigation justify utilizing a committee to review it.

Except in these situations, the Commissioner may, upon petition, waive institutional review for specific ongoing device studies, especially where a study was initiated several years before the proposed requirement becomes effective or if he concludes that institutional review is not required considering the degree of risk posed by the investigational study.

Numerous objections were received to the requirement of § 812.42(c)(2)(iv) of the August 20, 1976 proposal that the sponsor assure that the institutional review committee complies with the requirements of Subpart D (to be superseded by future FDA regulations establishing standards for institutional review boards). The Commissioner agrees that the proposed requirement was impractical and that the sponsor cannot supervise the daily activities of the institutional review committee. However, he does not believe that the sponsor can continue to rely on the institutional review committee's agreement to comply with FDA requirements once he learns that the committee does not meet FDA standards. Accordingly, in proposed § 812.55(f) FDA is requiring a sponsor to report to FDA when the sponsor learns that a committee is not complying with its agreement to review the study or with applicable FDA regulations. Such reports will enable FDA to discover when committees are not meeting their obligations and to decide whether the committee's process of review is adequate for FDA-regulated clinical investigations.

A comment on § 812.42(c)(2)(ix) of the August 20, 1976 proposal objected to the requirement that the sponsor maintain or assure that an investigator maintains the records of all submissions to and actions by the committee. As revised, proposed § 812.55(g) now merely requires the sponsor to maintain copies of all communications he has engaged in with the committee and with any investigator regarding the study.

SELECTION OF INVESTIGATORS

Proposed § 812.43(a) (21 CFR 812.43(a)) requires the sponsor to select qualified investigators.

Proposed § 812.43(b) requires the sponsor to obtain the investigator's signed statement, which includes an agreement to comply with FDA regulations and a description of his or her qualifications.

Two comments were received on proposed § 812.43(b)(1). One was that an investigator of devices should not be required to certify his or her credentials to FDA since an investigator of drugs does not have to meet this requirement. This comment argued that Parts 812 and 312 should be consistent. A second comment argued that the sponsor should obtain assurance statements from investigators, file them, and submit only the sponsor's assurance to FDA that the investigator's statement was on file.

The Commissioner believes that for enforcement reasons it is better for FDA to have copies of the signed undertaking of the investigator. Moreover, this requirement is imposed by section 520(g)(3)(C) of the act. For these reasons, the Commissioner rejects both comments.

Proposed § 812.43(b)(1)(vi) requires that the sponsor describe the specific experience of the investigator with the device to be investigated, including the date, amount and description of the experience, and the name of the institution where the device was investigated. This language is adopted from a useful comment suggesting that such information is relevant in selecting the

dergo such review unless circumstances clearly make it unnecessary, or infeasible, or inimical to the subject's interest. Therefore, he is proposing in § 812.42(b) and future agency-wide regulations to make review by an institutional review committee a general precondition to submission of any clinical investigation that is subject to require- that the sponsor assure that the institutional review committee complies with the requirements of Subpart D (to be superseded by future FDA regulations establishing standards for institutional review boards). The Commissioner agrees that the proposed requirement was impractical and that the sponsor cannot supervise the daily that the sponsor describe the specific experience of the investigator with the device to be investigated, including the date, amount and description of the experience, and the name of the institution where the device was investigated. This language is adopted from a useful comment suggesting that such information is relevant in selecting the

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investigator and passing on his qualifications.

Proposed § 812.43(b)(3) as revised clarifies that subordinate investigators who are responsible to the named investigator may participate in the study.

Proposed § 812.43(b)(4) requires the investigator to state whether any study or research that such investigator has been involved in has been discontinued by order of a sponsor, institutional review committee, or FDA. Comments objected that such disclosure may unfairly prejudice the selection of an investigator. The Commissioner disagrees. The selection of a qualified investigator will not be prejudiced by this provision since it functions only to alert those responsible for selecting investigators and approving investigators' qualifications to matters that may require consideration. The Commissioner does not intend that qualified investigators be excluded from studies simply because prior studies have been suspended or terminated for reasons that do not refect on the investigator's qualifications. The Commissioner does not believe a sponsor will refuse to include an investigator simply because a study was terminated for reasons unrelated to investigator qualifications. If this information is not required to be disclosed, the sponsor and FDA may be deprived of information relevant in evaluating the investigator's ability to conduct the proposed investigation. Accordingly, the Commissioner has retained the provision.

The Commissioner received a comment objecting to the provision of proposed § 812.43(b)(5), which requires the naming of other investigators who are to participate under the supervision of the lead investigator, because there might be frequent turnover among a sponsor's house staff that reports to a lead investigator. The Commissioner believes it essential that all investigators participating in the study be identified in records submitted to FDA.

CONTROL OVER THE INVESTIGATIONAL DEVICE; FACILITIES

Proposed § 812.45(a) requires the sponsor to ship the device only to investigators who have signed statements in accordance with § 812.43(b) to abide by FDA regulation. The sponsor must also comply with FDA requirements on control of investigational devices and assuring the adequacy of facilities (proposed Subparts C and F of Part 52), described in the September 27, 1977 proposed regulations on obligations of sponsors and monitors of clinical investigations.

Proposed § 52.108 requires the sponsor to maintain records of all shipments of the device to investigators. Comments on proposed § 812.45(c) of the August 20th proposal objected to this procedure on the grounds that section 520(j) of the act prohibits unnecessary traceability requirements. The comment further argued that there was nothing in the preamble that would justify the recordkeeping requirement.

The Commissioner believes that only by strict accounting for the devices received can the control over investigational devices intended by Congress be ensured. The Commissioner believes that it is, or should be, standard practice for many investigational devices to bear an identification number enabling the shipper to determine where that device was shipped by referring to a record of that number. The Commissioner notes that only one comment objected to this provision. The Commissioner concludes that traceability requirements for investigational devices are necessary to ensure the protection of the public health and are not unreasonable or unduly burdensome.

The Commissioner received comments that the language of § 812.45(d) of the August 20th proposal concerning the adequacy of facilities incorrectly implied that the device must be "safe and effective for testing" when it is the very purpose of the study to determine safety and effectiveness. The Commissioner agrees that this language was inappropriate and has not included it in proposed § 52.47.

Another comment argued that § 812.45(d) of the August 20th proposal effectively imposed a good manufacturing practice (GMP) requirement on investigational devices. Since the statute provides for investigational devices to be exempted from GMP's, the comment suggested that proposed § 812.45(d) be deleted.

The Commissioner believes that the comment reflects a misunderstanding of the act and the regulation. The effect of proposed § 52.47 (which replaces § 812.45(d) of the August 20th proposal) is not to require a sponsor to comply with GMP regulations issued under section 520(f) of the act where such a requirement would be inappropriate. Rather, the proposal that a sponsor assure the adequacy of testing facilities is a requirement that is necessary both for the protection of the public health and safety and for efficient enforcement of the act, under sections 520(g)(2)(B) and 701(a) of the act.

MONITORING THE INVESTIGATIONAL STUDY

Proposed § 812.46(a) requires the sponsor to comply with the requirements of 21 CFR 52.28 and the sponsor's monitor to comply with 21 CFR 52.29. Sections 52.28 and 52.29 were proposed in the September 27, 1977 proposed regulations on obligations of sponsors and monitors.

One comment questioned the use of the term "appropriately trained and qualified" with respect to the individual designated to monitor the study. The comment argued that the sponsor's monitor could be an administrator and need not be scientifically qualified. The Commissioner will consider this comment in developing a final regulation on proposed §§ 52.28 and 52.29.

One comment suggested that although one individual within a company should be held responsible for the investigation, that person should be permitted to use subordinates to assist in monitoring studies. Proposed § 52.23 now provides explicitly for a sponsor to designate more than one monitor.

Proposed § 812.46(b) clarifies the sponsor's responsibility in the event the sponsor discovers that an investigator has not complied with FDA regulations or with his or her agreement to conduct the study in accordance with this regulation. The sponsor is required to secure the investigator's compliance with the requirements of this part or discontinue shipments to such investigator. In addition, the sponsor may suspend or terminate any study that the investigator is performing for the sponsor. In some cases, an investigator may be brought into compliance without discontinuance of shipment or suspension of the study. A sponsor must act quickly to secure investigator compliance. The sponsor cannot permit the investigation to continue without a convincing assurance from the investigator that he or she will comply in the future. The sponsor's responsibility to monitor the study under proposed §§ 52.28, 52.29, and 812.46(b) is not discharged by merely obtaining an agreement to comply from the investigator.

Proposed § 812.46(b), as revised, differs somewhat from the August 20th proposal and is proposed on the Commissioner's initiative rather than in response to comments. No specific action was required of the sponsor by the August 20th proposal. The Commissioner wishes to stress that while a sponsor can, in good faith, rely on an investigator's agreement to comply with resgulations, once a sponsor discovers in any manner (either by monitoring or otherwise) that the investigator is no longer in compliance, the sponsor must act to secure compliance or suspend the study.

Proposed § 812.46(c)(1) requires the sponsor to undertake a special investigation whenever the sponsor learns of any serious adverse effect, death of subject, or life-threatening medical problem, that may reasonably be regarded as device-related. Once the sponsor has learned of any of these, the sponsor must relay the information to other investigators participating in the study and to FDA. The

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report must be made as soon as possible, but in no event later than 10 working days after the sponsor learns of the effect, death, or problem. This section was modified in response to comments arguing that only reactions which are both "device related" and "serious" should have to be reported. With respect to the term "device related," the Commissioner cautions that the term includes any reaction that may reasonably be regarded as caused by or associated with the device. This includes reactions associated with any part of an entire device system, including the packaging.

One comment proposed that special investigations be undertaken in cooperation with appropriate institutional officials and the investigator. The Commissioner expects that while a special investigation may often involve persons in addition to the sponosor, it is proper for FDA to place the primary responsibility on the sponsor to undertake such an investigation.

One comment suggested that an informal conference with the sponsor be held immediately if FDA suspends the study under § 312.46(c)(2). As indicated above, agency experience with prehearing conferences suggests that such conferences often become like formal hearings. The Commissioner believes that provision for a prehearing conference would unnecessarily delay the administrative process and would duplicate provisions for obtaining review of the withdrawal of an investigational device exemption. Accordingly, no provision is made for such an informal conference.

Several comments argued that the study should be suspended only after the sponsor has had the opportunity to assess adverse reactions. The Commissioner agrees that the point at which information is believed to exist which would warrant suspension of the study is initially a matter of the sponsor's judgement, although FDA or an institutional review committee may order suspension after reviewing the data. The Commissioner does not intend that a suspension be imposed automatically or that a suspension necessarily result in termination of a study. Only when the potential risks of continuation outwiegh the potential benefits should the study be terminated.

Each study must be assessed on its own merits. The Commissioner received a comment that the failure of a life-sustaining device in a study involving several subjects would not warrant the removal of that device from other subjects if removal would cause or threaten to cause the death of the ramaining subjects. The Commissioner agrees but believes it appropriate to provide that, after suspension, only those subjects whose medical needs require the continued use of the device may continue to receive the device. Also, no new subjects may be brought into the study.

The Commissioner believes that the 5 working days, or less, is not too short a period to suspend an investigation once sufficient information has been discovered to warrant suspension. The Commissioner did not intend to require that a study be suspended within 5 days on the basis of isolated adverse reports. The Commissioner does require the sponsor to investigate and correlate adverse information to determine whether it warrants suspension of the study. The Commissioner emphasizes that FDA may reverse the sponsor's decision not to suspend a study in appropriate cases.

Proposed § 812.46(d) prohibits sponsors from unduly prolonging a study. This paragraph was revised to respond to comments that FDA should not force a sponsor to submit a premarket approval application if the sponsor does not wish to do so. As revised, proposed § 812.46(d) provides that once data are developed which would support submission of an application for premarket approval, the sponsor must either submit such an application or discontinue the study. The sponsor is no longer required to give a statement of the sponsor's reasons for discontinuing the study without submitting an application for premarket approval to FDA.

One comment advocated that the sponsor be allowed to continue to provide the investigator with the device between the completion of the clinical trials and formal commercial marketing (e.g., while the premarket approval application is undergoing review).

The Commissioner advises that this practice will be permissible as long as the investigational device exemption is active while the premarket approval application is pending and the investigator remains a qualified investigator who complies with FDA regulations.

SUBMITTING INFORMATION TO INVESTIGATORS

Proposed § 812.47 requires the sponsor to provide all investigators with copies of the investigational plan, the report of prior investigations of the device, and labeling (including labels) for the device which shall meet the requirements of proposed § 812.5(b). Proposed § 812.47 does not apply to a sponsor-investigator who is the only investigator.

Proposed § 812.47(b) requires the sponsor to notify the investigator of the completion or discontinuance of the study or of the withdrawal of an exemption.

Proposed § 812.47(c) requires the sponsor to notify the investigator if a premarket approval application for the investigational device is granted.

One comment argued that there is no statutory basis for requiring the sponsor to notify the investigator if an application for premarket approval has been approved. The Commissioner believes it important for investigators to understand the regulatory status of products they use. Thus, the requirement is authorized under sections 520(g) and 701(a) of the act.

PROMOTION AND SALE OF AN INVESTIGATIONAL DEVICE

Proposed § 812.50(a) requires a sponsor to comply with 21 CFR 52.118. Proposed § 52.118, a section of the proposed regulations on obligations of sponsors and monitors, prohibits a sponsor from representing that an unmarketed investigational device is safe and effective for the purpose for which it is under investigation and from otherwise commercializing the device.

The Commissioner received several comments urging that the regulation not apply these requirements to devices for which the act provides a transitional period. The Commissioner has partially responded to these comments by not applying this requirement to lawful commercial shipments of devices during the transitional period under section 501(f)(2)(B) of the act. The requirement does, however, apply to all shipments for investigational use of devices, including devices previously regulated as new drugs that are subject to section 520(1) of the act.

Several comments defended the practice of making claims for safety when only the effectiveness of the device is being investigated. Such an investigation could occur where the device has a proven market history and is being investigated for a new use. Similarly, a device might be known to be effective but its safety might require further investigation.

The Commissioner believes that the concern expressed in the comments is partly addressed in proposed § 52.118. The Commissioner cautions that a maufacturer cannot make (1) claims of effectiveness for the purposes for which a device is under investigation if the device is being tested for effectiveness for those purposes, or (2) claims for safety for certain purposes if the device is being tested for safety for those purposes; or (3) claims for both safety and effectiveness for certain purposes if both safety and effectiveness for those purposes are under investigation.

Several comments were received on proposed § 812.50(b)(1) of the August 20, 1976 proposal which prohibited commercial distribution and test marketing of an investigational device or other commercialization until it has been approved for marketing for the purpose for which it is under investigation. (This restriction does not apply to lawful commercial shipments of Class III devices in commercial dis-

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tribution on or before May 28, 1976, or devices substantially equivalent to such devices, or to class I or II devices; the Commissioner has clarified that this restriction does apply to investigational devices in class III under section 520(1) of the act that were previously regarded as new drugs.)

One comment objected to a supposed restriction on test marketing of widely used consumer items since product testing to determine consumer attitudes is an important decision element in the company's operations plan. Once safety and effectiveness are proven, the comment argued, the company should be able to premarket test the device prior to incurring the cost of obtaining premarket approval of the device. The comment conceded that test marketing is not a substitute for adequate clinical testing and should not be a subterfuge to permit the commercial distribution of a product while the product is still undergoing testing or premarket approval. The comment urged that there be an opportunity for premarket testing before complying with sections 510(k) or 513(f) of the act.

In proposed § 812.2(b)(2) (21 CFR 812.2(b)(2)), the Commissioner has exempted from Part 812 test marketing of a device conducted solely to investigate consumer preference. Other test marketing can be accomplished under an investigational device exemption. The waiver provisions in § 812.10 provide a mechanism to avoid application of inappropriate requirements.

Proposed § 812.50(c) prohibits the sponsor from charging for use of the device if FDA finds the price to be unreasonable. This provision received several comments.

The Commissioner notes that traditionally FDA has rarely allowed a charge for an investigational new drug. The Commissioner concedes that the investment cost of developing a device may often be far greater than the cost of developing a new drug, and that the actual cost recovered by the manufacturer may be a factor in proceeding with development of the device. Thus, the Commissioner believes that it may be reasonable for a sponsor to recoup such sponsor's development cost, particularly for a high cost device, even while the device is being investigated.

However, because an effective means is needed to prevent commercialization of a device under the guise of recovering development costs, the Commissioner believes it necessary to retain a provision for FDA to find unreasonable the cost on an investigational device in particular cases. Evidence of profitmaking by means of charges for relatively inexpensive items may suggest that the device is actually being marketed prior to completion of the investigation in violation of the act and these regulations.

The Commissioner does not intend to substitute the Commissioner's judgment for that of the sponsor or manufacturer of the device as to the need to recoup development costs. The Commissioner will, however, determine whether the charge exceeds that necessary for appropriate recoupment. If the Commissioner finds that commercialization of the device is the actual objective of the charge, the Commissioner will notify the sponsor of this finding and that the application for an investigational device exemption is disapproved (or the exemption withdrawn) unless the sponsor agrees not to charge or to reduce the charge (and, where appropriate, to refund the charge). A sponsor who does not wish to eliminate or reduce the proposal to charge for the device may inform the agency of his interest in a regulatory hearing under the procedures in § 812.30(d) for disapproval of an application or, where appropriate, in § 812.35(b) for withdrawal of an investigational device exemption.

REPORTING TO FDA, MONITORING RECORDS, AND PERMITTING INSPECTION

Proposed § 812.55(a) requires the sponsor to maintain records on which to base reports to FDA. Reports are required to be made at appropriate intervals not exceeding 1 year.

Proposed § 812.55(b) requires the sponsors to notify FDA within 30 days of completion, termination, or discontinuation of the study (including withdrawal of the exemption). A final report is required to be furnished to FDA within 6 months after the study is concluded.

Proposed § 812.55(c) requires the sponsor to notify FDA whenever the sponsor requires investigators to return or dispose of the supplies of the device and of steps taken to comply with the provisions for alternate disposition of the device found in proposed § 52.114, a provision of the proposed regulations on obligations of sponsors and monitors of clinical investigations.

Proposed § 812.55(d) requires the sponsor to report to FDA a serious adverse reaction (including death or life-threatening medical problem) that is subject to the requirement of a special investigation and that occurs during the course of the study.

Proposed § 812.55(d) or § 812.55(c) in the August 20, 1976 proposal) was the subject of several comments. One comment argued that the meaning of "adverse" was unclear and asked how adverse the reaction must be for it to be reportable. The Commissioner has qualified this requirement so that only "serious" adverse effects will trigger the reporting requirement. Other comments were that the reporting period is too short and should be extended to 10, 15, or 30 days. The Commissioner has lengthened to 10 working days the period for reporting results to FDA, to conform to future agency regulations on responsibilities of investigators.

Another comment suggested that if an institutional review committee is monitoring the investigation, the sponsor need not provide FDA with the report of special investigation. The Commissioner disagrees. The notification to FDA is necessary; FDA is the repository of all information regarding the application, together with information relating to similar studies, and is in a better position than any individual institutional review committee to make findings both with respect to the study from the standpoint of national standards for device investigations, and with respect to other related studies of which a particular institutional review committee may be unaware.

Proposed § 812.55(e) requires the sponsor to submit to FDA a copy of any investigator's determination that informed consent could not be obtained from the subject. The report is required to be submitted within 5 working days after the sponsor receives the report of the determination from the investigator. One comment suggested extending the reporting period to 30 days. The Commissioner believes that extending the period to 30 days might make it more difficult to reconstruct the precise events by questioning subjects should an investigation be required.

The Commissioner believes that the requirement for informed consent is important and that deviations from informed consent warrant immediate notification.

Proposed § 812.55(f) requires a sponsor to report to FDA any discovery that an institutional review committee is not complying with its agreement to review the study or with applicable FDA regulations.

Proposed § 812.55(g) requires the sponsor to keep records of all applications, reports, and correspondence that the sponsor submits to FDA and of all communications between the sponsor and any institutional review committee or investigator regarding the study.

Proposed § 812.55(h) permits a sponsor to withdraw from recordkeeping requirements by transferring custody to another person. Notice of transfer of custody must be given to FDA.

Proposed § 812.55(i) authorizes FDA and the institutional review committee or their authorized representatives to inspect sponsor records and facilities. Proposed § 812.55(i) (§ 812.55(h) in the August 20, 1976 proposal) has been changed to clarify the authority of the sponsor to withhold from inspection by the institutional review committee trade secret or commercial or financial information that is confidential, as described in 21 CFR 20.61. This change

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was made in response to comments that the institutional review committee should not have access to a sponsor's trade secrets and concern that rival investigators and sponsors might gain access to proprietary information by means of membership on an institutional review committee. The Commissioner emphasizes that the committee may need to have access to safety and effectiveness data and that an institutional review committee is not required to approve a study when it lacks the data it requires for a proper determination of whether it is safe to begin or continue trials with human subjects.

Other comments argued that a sponsor's financial records should be exempt from FDA inspection. The Commissioner responds that financial records are relevant to determine whether or not a device is being commercially marketed and are required to be made available for inspection by FDA for that purpose.

Another comment argued that the sponsor should be responsible only for providing access to those facilities over which the sponsor has physical control, e.g., not those of investigators or government agencies. The Commissioner clarifies that this section is not to be interpreted to require the sponsor to provide access to material where the sponsor lacks authority to provide for such access.

Other comments expressed the view that FDA should be able to copy only those records relevant to the study under investigation. The Food and Drug Administration will only exercise its authority to copy records when these records are relevant to the study, but maintains that the initial judgment as to relevance must be FDA's rather than the sponsor's.

Comments expressed concern about the confidentiality of patient names in records subject to FDA inspection. The Commissioner perceives no conflict between these provisions and the DHEW regulation on protection of human subjects, 45 CFR Part 46, for the confidentiality of patient data. Although the Commissioner reasserts his right to inspect and obtain patient names when appropriate, the Commissioner recognizes that the issue may be decided by future legislation or other FDA regulations and that investigators have legitimate ethical concerns about protecting patient confidentiality, which FDA will carefully weigh before requiring patient data to be provided. The Commissioner regards exercise of the Commissioner's authority to obtain patient names as an unusual step, but one which the Commissioner may need to take in certain circumstances where necessary to protect the health of subjects or assure the validity of data.

A comment on proposed § 812.55(j) (§ 812.55(i) in the August 20, 1976 proposal) argued that the requirement for the sponsor to submit "any records" is too broad and should be narrowed. The Commissioner has the authority to require relevant records, but because the Commissioner cannot foresee which records may be required, the Commissioner believes the present language is appropriate.

Practical Difficulties in Determining the Sponsor Relationship

The Commissioner received a comment arguing that there are practical difficulties in determining when a manufacturer is actually a sponsor within the meaning of the regulation. The comment cited the examples of an investigator who continues clinical testing of a device after the sponsor has suspended or discontinued a sponsored investigation, or who requests a sample of a marketed device from a sponsor for the purpose of testing a new use, or who conducts tests during the course of a sponsored investigation which were not part of the sponsor's investigational plan. The comment expressed concern that manufacturers might become sponsors involuntarily because of unauthorized actions by an investigator. The comment argued that the term "sponsor" should not include a person who might otherwise be considered a sponsor but who obtains a written agreement from the investigator that the investigator is a sponsor-investigator.

The Commissioner agrees. The agency generally does not object to an investigator assuming the responsibilities of a sponsor and has explicitly recognized the existence and status of sponsor-investigators in the September 27, 1977 proposed regulations on obligations of sponsors and monitors of clinical investigations. Nor does the Commissioner generally object to a manufacturer employing contractual or other means to clarify his relations with investigators or with respect to particular investigations which the manufacturer does not wish to sponsor. However, the Commissioner cautions that the actual relationship between the parties may be examined to determine whether the relationship between the parties is as described. The Commissioner would be concerned if a device manufacturer's efforts to avoid responsibility for device studies resulted in undue risks to subjects or undermined the validity of the data from the studies. In such cases, FDA may inform the manufacturer to cease shipments of the investigational device if the manufacturer is unwilling to assume the responsibilities of a sponsor. Aside from these concerns, however, manufacturers and investigators are free to tailor their relationships to their own needs.

The Commissioner also cautions that the question of who serves as a sponsor under proposed Part 812 is not intended to have any bearing on liability questions in product liability lawsuits.

Responsibilities of Institutional Review Committees

Subpart D of the August 20th proposal concerning the responsibilities of institutional review committees will be superseded by a future FDA regulation applicable to clinical investigations of drugs, devices, and other articles. The substance of the future regulation is largely found in existing regulations in 21 CFR Part 312 and 45 CFR Part 46, as well as portions of the August 20th proposal. Comments on Subpart D are being considered by the internal FDA task force responsible to the Commissioner for the preparation of this document. Until the future FDA regulation is promulgated as a final order, Subpart D of the August 20th proposal can be followed as a guideline for device studies.

Responsibilities of Investigators

Subpart E of the August 20th proposal concerned the responsibilities of investigators and will be superseded by an FDA proposed regulation on clinical investigators of drugs, devices, and other articles, which will be published in the Federal Register in the near future. Comments on Subpart E are being considered by the internal FDA task force responsible for preparation of this proposal, which, until the future FDA regulation is promulgated, can be followed as a guideline for device studies.

Informed Consent

Several comments objected to the informed consent requirement as it related to in vitro diagnostic products. The Commissioner believes that those comments are effectively met by the exemption in proposed § 812.2(b)(5) of most in vitro diagnostic products from the requirements of this regulation.

The Commissioner received few other comments on proposed Subpart F. Some comments argued that FDA should await the result of the study of informed consent being conducted by the National Commission for the Protection of Human Subjects in Biomedical and Behavioral Research. The Food and Drug Administration has been in contact with the staff of the National Commission and has received materials from them and placed these materials on public display in the Hearing Clerk's Office. However, because Congress has mandated that regulations relating to investigational devices be published promptly, and the National Commission will not make its report on informed consent in the immediate future, the Commissioner has decided not to wait for the

be provided. The Commissioner regards exercise of the Commissioner's authority to obtain patient names as an unusual step, but one which the Commissioner may need to take in certain circumstances where necessary to protect the health of subjects or assure the validity of data.

A comment on proposed § 812.55(j) (§ 812.55(i) in the August 20, 1976 proposal) argued that the requirement for the sponsor to submit "any records" is too broad and should be narrowed. The Commissioner has the authority to require relevant records, but because the Commissioner cannot foresee which records may be required, the Commissioner believes the present language is appropriate.

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The Commissioner received a comment arguing that there are practical difficulties in determining when a manufacturer is actually a sponsor within the meaning of the regulation. The comment cited the examples of an investigator who continues clinical testing of a device after the sponsor has suspended or discontinued a sponsored investigation, or who requests a sample of a marketed device from a sponsor for the purpose of testing a new use, or who conducts tests during the course of a sponsored investigation which were not part of the sponsor's investigational plan. The comment expressed concern that manufacturers might become sponsors involuntarily because of unauthorized actions by an investigator. The comment argued that the term "sponsor" should not include a person who might otherwise be considered a sponsor but who obtains a written agreement from the investigator that the investigator is a sponsor-investigator.

The Commissioner agrees. The agency generally does not object to an investigator assuming the responsibilities of a sponsor and has explicitly recognized the existence and status of sponsor-investigators in the September 27, 1977 proposed regulations on obligations of sponsors and monitors of clinical investigations. Nor does the Commissioner generally object to a manufacturer employing contractual or other means to clarify his relations with investigators or with respect to particular investigations which the manufacturer does not wish to sponsor. However, the Commissioner cautions that the actual relationship between the parties may be examined to determine whether the relationship between the parties is as described. The Commissioner would be concerned if a device manufacturer's efforts to avoid responsibility for device studies resulted in undue risks to subjects or undermined the validity of the data from the studies. In such cases, FDA may inform the manufacturer to cease shipments of the investigational device if the manufacturer is unwilling to assume the responsibilities of a sponsor. Aside from these concerns, however, manufacturers and investigators are free to tailor their relationships to their own needs.

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materials from them and placed these materials on public display in the Hearing Clerk's Office. However, because Congress has mandated that regulations relating to investigational devices be published promptly, and the National Commission will not make its report on informed consent in the immediate future, the Commissioner has decided not to wait for the

National Commission to publish its recommendations. The Commissioner will, of course, consider any proposals made in the final report of the National Commission as they relate to the protection of human subjects and will make appropriate revisions in the proposed regulation after it is made final. Other revisions of Subpart F may occur if the Commissioner decides to promulgate general informed consent regulations applicable to clinical investigations of drugs, devices, and other articles.

Several comments argued that the requirement of informed consent should be related to the degree and nature of the risk presented to patient safety and privacy. The Commissioner agrees but believes that this flexibility is inherent in Subpart F.

Several comments argued that the regulations should provide for oral informed consent in certain cases. Most of these comments concerned studies of in vitro diagnostic products and have been addressed by the exemption of many such products from proposed Part 812. Although no provision for oral informed consent is being proposed, the Commissioner invites comments on a procedure, set out below as possible proposed § 812.123(c), that would enable an investigator to certify in writing that oral consent was obtained from the subject or the subject's legal representative. Use of the certification procedure would be limited to situations in which the device is both a nonvital device and is used in a low risk study, under a notification rather than an application for an investigational device exemption.

(c) (1) With the approval of the sponsor and the institutional review committee, the investigator may make a written record certifying that he has obtained the oral informed consent of the subject (or, where appropriate, the subject's legal representative) when the study involves a nonvital investigational device used in a low risk study for which the sponsor has submitted a notification under § 812.20, and the Food and Drug Administration's letter under § 812.20(c)(1) informing the sponsor of the date of receipt does not also inform the sponsor that (i) an application, rather than a notification, is required, (ii) that the agency disagrees with the determination as to whether the device is vital or with the determination as to risk assessment, or (iii) that written consent in accordance with paragraph (c) of this section shall be obtained.

(2) Where the certification procedure is permitted to be used, the investigator may certify that such investigator has obtained the oral informed consent either of a group of subjects or of every subject. Where the study involves repetitive procedures, e.g., the subsequent use of the same test, oral informed consent may be documented by a single record certifying that consent was obtained for the initial procedure and the subject, or group of subjects, was advised that the procedure might be repeated and of the approximate number of times the procedure might be performed. When the study involves additional, nonrepetitive procedures, e.g., different tests, involving a subject at a time later than when oral informed consent is obtained initially, the subject's oral informed consent shall be separately documented when each such additional procedure occurs.

(3) A certification shall detail all the information given to each subject to obtain the subject's oral informed consent and shall be signed by the investigator. The certification shall be maintained in the investigator's records for the time prescribed in § 52.195 of this chapter.

GENERAL REQUIREMENTS OF INFORMED CONSENT

Proposed § 812.120 sets forth the general requirements for obtaining informed consent.

One comment suggested there should be some means of obtaining consent of an illiterate subject who is not under a legal disability.

The Commissioner believes that written informed consent generally can be obtained from an illiterate individual who wishes to consent to use of an investigational device. In general, an illiterate but competent individual should have the same access to an investigational device as does a literate person. Where an individual from whom informed consent is sought is of limited literacy, the investigator should read the written agreement to the individual and obtain the individual's signature or mark. If an illiterate subject also has limited capacity to give informed consent (e.g., because of mental retardation), the investigator should obtain informed consent from the subject's representative. The Commissioner invites public comment whether the approach described here adequately covers those situations where written informed consent to use an investigational device would have to be obtained from an illiterate individual; whether there are likely to be illiterate subjects or representatives of subjects who are incapable of signing their names or marks; and, if so, whether there should be either a provision for independent witnesses to attest that the agreement was read to the illiterate and that the illiterate consented to use of the device, or an exception in emergency cases from the requirement that the consenting individual sign the written agreement, or both.

Another comment suggested that existing DHEW rules on the elements of informed consent are sufficient for this regulation. The Commissioner disagrees. The additional requirements found in this section were required in light of the legislative history of the act (House Report No. 94-1090, Conference Report on Medical Device Amendments of 1976, May 6, 1976, at p. 64), which lists elements of informed consent that the congressional conferees on the legislation believed should be included. Accordingly, proposed § 812.120 continues to provide for elements of informed consent in addition to those required in 45 CFR Part 46.

Another comment suggested that making exceptions to written consent should be the prerogative not of FDA but of the institutional review committee. The Commissioner believes that because of the inherent differences among investigational review committees, and the varying performance of such committees, it is not acceptable to leave the determination of when an exception may be granted entirely to the discretion of individual institutional review committees. An institutional review committee may properly reject a determination by an investigator that an exception to the requirement for written evidence of consent is appropriate. However, the Commissioner believes that to grant the institutional review committee discretion to dispense with the requirement for a written consent, without FDA review of this decision, would deprive human subjects of the protection that Congress intended them to have.

Accordingly, proposed § 812.120(c) provides that informed consent shall be evidenced by a written agreement, signed by the subject or the subject's legal representative.

One other change suggested in proposed § 812.120 was that the term "legally effective informed consent" read only as "informed consent" since the term "legally effective" adds nothing to the requirement. The Commissioner has retained the term since it appears in the DHEW Guidelines, for reasons stated in the preamble to Subpart B.

EXCEPTION FROM REQUIREMENT

Proposed § 812.123 was altered in only one way. The term "effective" has been inserted before the term "alternative" in paragraph (a)(2) so that the investigator must determine, among other things, that there is no effective alternative method of therapy that is approved or generally recognized which may save the life of the subject. The purpose of this change is to provide that the therapy that is available as an alternative must be an effective therapy, not additional therapy that is not likely to produce effective results. This change is in response to comments that the therapy ought to be more likely to save the subject's life or aid the patient rather than merely be an alternative.

Other comments suggested deletion of the required determination that no alternative therapy exists, as it goes beyond the language of section 520(g)(3) of the act and would significantly decrease the use of the procedure contemplated. The Commissioner has determined that information on alternative therapy is needed in in-

certify that such investigator has obtained the oral informed consent either of a group of subjects or of every subject. Where the study involves repetitive procedures, e.g., the subsequent use of the same test, oral informed consent may be documented by a single record certifying that consent was obtained for the initial procedure and the subject, or group of subjects, was advised that the procedure might be repeated and of the approximate number of times the procedure might be performed. When the study involves additional, nonrepetitive procedures, e.g., different tests, involving a subject at a time later than when oral informed consent is obtained initially, the subject's oral informed consent shall be separately documented when each such additional procedure occurs.

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Another comment suggested that existing DHEW rules on the elements of informed consent are sufficient for this regulation. The Commissioner disagrees. The additional requirements found in this section were required in light of the legislative history of the act (House Report No. 94-1090, Conference Report on Medical Device Amendments of 1976, May 6, 1976, at p. 64), which lists elements of informed consent that the congressional conferees on the legislation believed should be included. Accordingly, proposed § 812.120 continues to provide for elements of informed consent in addition to those required in 45 CFR Part 46.

Another comment suggested that making exceptions to written consent should be the prerogative not of FDA but of the institutional review committee. The Commissioner believes that because of the inherent differences among investigational review committees, and the varying performance of such committees, it is not acceptable to leave the determination of when an exception may be granted entirely to the discretion of individual institutional review committees. An institutional review committee may properly reject a determination by an investigator that an exception to the requirement for written evidence of consent is appropriate. However, the Commissioner believes that to grant the institutional review committee discretion to dispense with the requirement for a written consent, without FDA review of this decision, would deprive human subjects of the protection that Congress intended them to have.

Accordingly, proposed § 812.120(c) provides that informed consent shall be evidenced by a written agreement, signed by the subject or the subject's legal representative.

One other change suggested in proposed § 812.120 was that the term "legally effective informed consent" read only as "informed consent" since the term "legally effective" adds nothing to the requirement. The Commissioner has retained the term since it appears in the DHEW Guidelines, for reasons stated in the preamble to Subpart B.

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Other comments suggested deletion of the required determination that no alternative therapy exists, as it goes beyond the language of section 520(g)(3) of the act and would significantly decrease the use of the procedure contemplated. The Commissioner has determined that information on alternative therapy is needed in in-

formed consent forms for the protection of public health and safety, authorized in section 520(g)(2)(B) of the act. The Commissioner believes it appropriate to retain the alternative therapy provision, modified as described above.

Another comment argued that some subjects do not wish to be advised of the risks and benefits of the study being performed. The Commissioner is unable to see how the statutory requirement of obtaining informed consent can be met if the subject is not advised of the risks and benefits involved in the study. Regardless of the desires of the subject, there must be compliance with the statutory requirement with respect to investigational use of devices, that subjects involved in an experimental study be advised of the risks and benefits of the study so that their informed consent can be obtained.

A final comment noted that the time for determining in writing whether the situation was life-threatening should be after, not at the time of, the emergency. The Commissioner agrees that the determination of emergency may be reduced to writing by the investigator after the emergency situation has been treated.

ELEMENTS OF INFORMED CONSENT

Proposed § 812.130 has not been changed.

The Commissioner received several comments objecting to the use of the term "research." Substitution of the term "study" was suggested because it was felt that the subjects might equate "research" with "experimentation." The Commissioner sees no difference between the terms "research," "experimentation," and "study" and does not object to use of any of these terms in informed consent forms since the same idea is conveyed by all of these terms. There is no reason to change the proposal to achieve this flexibility. However, the Commissioner cautions against the substitution of euphemisms that disguise the investigational nature of the experiment. One way or another, the subject must be told that the device is an experimental device whose safety and effectiveness are not known and whose safety and/or effectiveness are currently the subject of investigation.

One comment was received on proposed § 812.130(a)(7) objecting to the requirement of informing subjects of the number of patients or subjects involved in the investigational study. The Commissioner believes that the number of subjects involved in an investigational study is relevant to the subject in assessing the risk to himself or herself. A subject might decline to participate in a study in which he or she was the only subject or one of a very small number of subjects. This information is relevant to the subject's assessment of the risks involved and should not be omitted. Furthermore, Congress specifically prescribed that one of the elements of informed consent was a description of the number of subjects involved (Conference Report, p. 64).

One comment argued that the requirement for informed consent in all testing of devices will effectively curtail testing of so-called "me-too" devices, e.g., devices which are substantially equivalent to old devices. However, Congress elected to provide a licensing system for class III devices that requires manufacturers to establish individually the safety and effectiveness of their products. The Commissioner believes that he must give effect to the statute and its legislative history by requiring informed consent in any investigational study subject to the regulation and believes it proper for subjects to be told when they are part of an experiment.

TESTS THAT DO NOT INVOLVE HUMAN SUBJECTS

Subpart H relates to devices intended for nonclinical tests and was not controversial. Subpart H was not changed, except that a new paragraph (a)(4) was added to proposed § 812.160 requiring that the device be tested in accordance with any applicable regulations in proposed 21 CFR Part 58, regarding good laboratory practices, published in the FEDERAL REGISTER of November 19, 1976 (41 FR 51206).

REFERENCES

Backgrougnd data and information on which the Commissioner relies in proposing this tentative final regulation and comments on the August 20, 1976 proposal have been placed on file for public review in the office of the Hearing Clerk (HFC-20), Food and Drug Administration, Room 4-65, 5600 Fishers Lane, Rockville, Md. 20857. This file includes memoranda of meetings between FDA employees and individuals outside FDA and representatives of other agencies, such as the National Institutes of Health and the following:

1. "Federal Control of New Drug Testing is Not Adequately Protecting Human Subjects and the General Public," General Accounting Office, July 15, 1976.

2. House Report No. 94-853, Medical Device Amendments, February 29, 1976 (Committee on Interstate and Foreign Commerce).

3. House Report No. 94-1090, Medical Device Amendments, May 6, 1976 (Conference Committee).

PROPOSED EFFECTIVE DATE

To provide interested parties an opportunity to begin clinical investigations prior to the effective date of the final regulation based on this tentative final regulation, FDA will accept applications for investigational device exemptions, if the applicant complies with the requirements set forth in the proposed regulation or, where different, this tentative final regulation.

Although applications may be submitted and will be processed, sponsors of investigational studies of devices are not required by law to submit applications before the final regulation is effective, and FDA is not obligated to respond within the 30-day period set forth in proposed §§ 812.20 or 812.21. Accordingly, until the final regulation becomes effective, a sponsor should not construe FDA silence as an approval of the application even if the 30-day period has elapsed. The Food and Drug Administration will attempt to notify sponsors that an application for exemption has been approved.

The Commissioner also cautions that changes in the final regulation may necessitate requiring a sponsor who relied on this tentative final regulation to submit additional information.

OPPORTUNITY FOR COMMENT AND PUBLIC HEARING

The final regulation will be published in the FEDERAL REGISTER after consideration of all comments submitted pursuant to this tentative final regulation and after an informal legislative hearing has been held at the end of the comment period pursuant to FDA's administrative practices and procedures regulations under Part 15 (21 CFR Part 15). Interested persons shall file a written notice of participation on or before June 12, 1978. In the event that no notice of appearance is filed, no hearing will be scheduled. A separate FEDERAL REGISTER notice will announce the exact date, time, and place of the hearing.

The Commissioner has carefully considered the environmental effects of the proposed regulation as revised in this tentative final regulation and, because the proposed action will not significantly affect the quality of the human environment, has concluded that an environmental impact statement is not required. A copy of the environmental impact assessment is on file with the Hearing Clerk, Food and Drug Administration.

Several comments argued that the proposal would have a serious adverse impact on the cost of conducting research on devices and thus, ultimately, on the prices charged consumers for devices. The Commissioner is sensitive to these concerns and believes the changes made to narrow the scope of the document and to provide an abbreviated application procedure will greatly reduce the industry's aggregate cost of complying with investigational device regulations. The Commissioner has not received any informa-

the number of patients or subjects involved in the investigational study. The Commissioner believes that the number of subjects involved in an investigational study is relevant to the subject in assessing the risk to himself or herself. A subject might decline to participate in a study in which he or she was the only subject or one of a very small number of subjects. This information is relevant to the subject's assessment of the risks involved and should not be omitted. Furthermore, Congress specifically prescribed that one of the elements of informed consent was a description of the number of subjects involved (Conference Report, p. 64).

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The Commissioner also cautions that changes in the final regulation may necessitate requiring a sponsor who relied on this tentative final regulation to submit additional information.

tion to justify a change in his conclusion that the proposal, as revised in this tentative final regulation, does not contain a major proposal requiring preparation of an economic impact statement under Executive Order 11821 and OMB Circular A-107.

Therefore, under the Federal Food, Drug, and Cosmetic Act (secs. 301, 501, 502, 520, 701(a), 702, 704, 801(d), 52 Stat. 1042-1043 as amended, 1049-1051 as amended, 1055-1057 as amended, 90 Stat. 565-574, 587 (21 U.S.C. 331, 351, 352, 360j, 371(a), 372, 374, 381)) and under authority delegated to him (21 CFR 5.1), the Commissioner proposes to amend Chapter I of Title 21, of the Code of Federal Regulations as follows:

PART 16—REGULATORY HEARING BEFORE THE FOOD AND DRUG ADMINISTRATION

1. By revising § 16.1(b)(28) to read as follows:

§ 16.1 Scope.

* * * * *

(b) * * *

(28) Sections 812.30(d), 812.35(b), and 812.170 relating to approval, disapproval, or withdrawal of approval of an investigational device exemption.

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PART 20—PUBLIC INFORMATION

2. Be revising § 20.100(c)(30) to read as follows:

§ 20.100 Applicability; cross-reference to other regulation.

* * * * *

(c) * * *

(30) Investigational device exemptions in § 812.38 of this chapter.

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3. By adding new Part 812 to read as follows:

PART 812—INVESTIGATIONAL DEVICE EXEMPTIONS

Subpart A—General Provisions

Sec.
812.1 Scope.
812.2 Applicability.
812.3 Definitions.
812.5 General qualifications for an exemption.
812.10 Petitions for waiver of requirements.
812.12 Information previously submitted.
812.19 Requirements applicable to importers and exporters of investigational devices.

Subpart B—Notifications and Applications for Exemption for Investigational Studies Involving Human Subjects

812.20 Notification.
812.21 Application.
812.25 Investigational plan.
812.27 Report of prior investigations of a device.
812.30 Food and Drug Administration review of and action on an application.
812.35 Withdrawal of an exemption.
812.38 Confidentiality of data and information in an application.
812.39 Supplemental applications and submissions concerning applications.

Subpart C—Sponsor Responsibilities in Investigational Studies Involving Human Subjects

812.40 General.
812.42 Review of the investigational study by the Food and Drug Administration and the institutional review committee.
812.43 Selection of investigators.
812.45 Control over the investigational device; facilities.
812.46 Monitoring the investigational study.
812.47 Submitting information to investigators.
812.50 Promotion and sale of investigational devices.
812.55 Reporting to the Food and Drug Administration, Maintaining records, and permitting inspections.

Subparts D and E—[Reserved]

Subpart F—Informed Consent of Human Subjects

812.120 General requirements of informed consent.
812.123 Exception from requirement.
812.130 Elements of informed consent in agreement.

Subpart G—[Reserved]

Subpart H—Tests That Do Not Involve Human Subjects

812.160 Conditions of exemption.
812.170 Termination of exemption.

AUTHORITY: Secs. 301, 501, 502, 520, 701(a), 702, 704, 801(d), 52 Stat. 1042-1043 as amended, 1049-1051 as amended, 1055-1057 as amended, 90 Stat. 565-574, 578 (21 U.S.C. 331, 351, 352, 360j, 371(a), 72, 374, 381(d)).

Subpart A—General Provisions

§ 812.1 Scope.

(a) This part implements section 520(g) of the act and provides that a device may be exempted from any of the requirements of the act enumerated in paragraph (c) of this section that would otherwise be applicable to the device, to permit investigational studies of the device by experts who are qualified by scientific training and experience to investigate the safety and effectiveness of devices intended for human use.

(b) This part has two objectives:

(1) To encourage the discovery and development of useful devices by applying special requirements to investigational studies of devices in lieu of those otherwise applicable requirements that may impede such discovery and development.

(2) To protect the public health and safety by assuring adequate safeguards for human subjects in investigational studies, by requiring studies to be conducted in conformity with ethical standards, and by fostering the development of reliable data concerning the safety and effectiveness of devices.

(c)(1) In general, an approved notification or application under § 812.30 exempts a shipment of a device for investigational use from provisions of the following sections of the act and regulations thereunder: Misbranding under 502, registration and premarket notification under 510, performance standards under 514, premarket approval under 515, records and reports under 519, restricted device requirements under 520(e), good manufacturing practice requirements under 520(f), and color additive requirements under 706.

These sections of the act and regulations thereunder apply to commercial shipments of a device that was in commercial distribution before May 28, 1976, or is substantially equivalent to such a device, and that is being commercially distributed at the same time the device is being investigated under this part.

(2) A device shall not be exempted from a provision of the act listed in paragraph (c)(1) of this section if the Commissioner determines that it is not exempt from such a provision in an order of approval or disapproval under § 812.30.

(3) A shipment of a device may be exempted from a banned device regulation under section 516 of the act if the Commissioner has approved an application for such an exemption under § 812.30(a)(2).

§ 812.2 Applicability.

This part applies as follows:

(a) *Studies subject to this part.* This part applies to:

(1) Any investigational device used in an investigational study involving human subjects for the purpose of determining whether the device is safe and/or effective, unless excluded by paragraph (b) or (d) of this section.

(2) Any investigational study concerning a device, except as otherwise provided in this section, whether it is undertaken to develop data to obtain approval for commercial distribution of a device (e.g., by approval under section 515 of the act), to conduct fundamental research involving human subjects for such scientific purposes as expanding medical knowledge but not for the purpose of obtaining approval for commercial distribution, or to aid diagnosis and treatment by means of use of an investigational device involving a human subject.

(3) An investigational study of a device pursuant to a product development protocol under section 515(f) of the act.

(b) *Studies not subject to this part.* Although studies described in this

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812.20 Notification.

development of useful devices by applying special requirements to investigational studies of devices in lieu of those otherwise applicable requirements that may impede such discovery and development.

(2) To protect the public health and safety by assuring adequate safeguards for human subjects in investigational studies, by requiring studies

for the purpose of obtaining approval for commercial distribution, or to aid diagnosis and treatment by means of use of an investigational device involving a human subject.

(3) An investigational study of a device pursuant to a product development protocol under section 515(f) of the act.

(b) *Studies not subject to this part.* Although studies described in this

paragraph are not subject to this part, they may be subject to other requirements of the act or this chapter, e.g., the requirements in section 515 of the act regarding premarket approval, in Part 58 concerning good laboratory practices for nonclinical studies, in Part 809 regarding in vitro diagnostic products, and in Part 820 of this chapter concerning good manufacturing practices. This part does not apply to:

(1) An experiment involving use of a device in a manner and for a purpose which is included in labeling specifically prescribed for such device by regulation under the act or labeling approved under section 507 or 515 of the act.

(2) Test marketing of a device where the only testing involved is that of consumer preference. (Where consumer preference testing is coupled with or designed to accomplish testing of the safety or effectiveness of the device, the testing is subject to this part.)

(3) The modification of an existing device for purposes other than testing its safety and effectiveness.

(4) The conjunction of two lawfully marketed devices to form a third device unless the purpose of joining the devices is to investigate the safety and effectiveness of the modification. However, this part applies when a study is performed to determine the safety or effectiveness of an approved or marketed device or the joining of several such devices for a new use.

(5) Devices for diagnosis of any human disease or condition (including in vitro diagnostic products) which are not invasive (e.g., do not penetrate or pierce the skin or mucus membranes of the body or the urethra, or the mouth beyond the pharynx, or the anal canal beyond the rectum, or the vagina beyond the cervical os), do not introduce energy into the subject, and are not used in the diagnosis of any disease or other condition in the subject without confirmation by use of a diagnostic device or procedure whose effectiveness for such diagnosis is established.

(6) Any device intended for veterinary use. However, devices ultimately intended for human use, but which are being tested in animals, shall comply with Subpart H of this part and with applicable requirements in Part 58 of this chapter.

(c) *Vital and nonvital investigational devices.* The controls applicable to an investigational device vary, as described in §§ 812.20 and 812.21, depending on:

(1) The importance of the diagnostic or therapeutic uses of the device (i.e., whether a device is vital or nonvital), and

(2) The degree of risk presented by the device to the subjects participating in the study (i.e., substantial risk or low risk).

(d) *Custom devices*—(1) *Requirements.* This part does not apply to a device if all of the following requirements are met:

(i) The device necessarily deviates from generally available devices to comply with the order of a health professional designated in paragraph (d)(2) of this section.

(ii) The device is not generally available in finished form for purchase or for dispensing upon prescription.

(iii) The device is not offered through labeling or advertising by the manufacturer, importer, or distributor thereof for commercial distribution.

(iv) The device is intended (*a*) for use by an individual patient named in the health professional's order and is to be made in a specific form for that patient, or (*b*) to meet the special needs of the health professional in the course of his or her practice.

(v) The device is not generally available to or generally used by other such health professional.

(vi) The device is made of safe and suitable materials (if an implant) and is not being used in a investigational study for the purpose of determining whether the device is safe or effective.

(vii) The Commissioner has not made an administrative determination that the device is subject to this part.

(2) *Health professionals.* A health professional authorized to use custom devices in accordance with this paragraph (d)(2) includes any licensed physician or dentist.

(3) *Examples.* The following examples illustrate the application of this paragraph.

(i) Alteration of an available device (for which sufficient information exists to determine that the device is safe and effective) to meet individual needs of patient or professional: A device that does not represent a new concept, and that is not being tested for safety and effectiveness, is available as a stock item off the shelf; the health professional orders the device and alters it, or has it altered, to meet the patient's, or the health professional's own, individual anatomical features (e.g., dimensions or disability). The basic device that is being customized in this manner is subject to the act and other requirements of this chapter (e.g., registration, classification, performance standards if class II, premarket approval if class III, good manufacturing practice regulations, etc.). However, the individual customizing of the device does not render it an investigational device subject to this part if the requirements of paragraph (d)(1) of this section are met.

(ii) Fabrication of a device (for which sufficient information exists to determine that the device is safe and effective) to meet individual needs of a patient or health professional: A manufacturer fabricates devices for health professionals, or a health professional fabricates devices, according to each individual patient's or health professional's anatomical features (e.g., using X-rays); the device does not involve new implant materials and does not otherwise represent a new concept. As in paragraph (d)(3)(i) of this section, the basic device that is being customized in this manner is subject to the act and other requirements of this chapter. However, the individual customizing of the device does not render it an investigational device subject to this part if the requirements of paragraph (d)(1) of this section are met.

(iii) Testing of a device (for which insufficient information exists to determine whether the device is safe and effective) for general use that will require individual customizing: A device that represents a new concept is being tested for safety and effectiveness; the device, by its nature, requires customization to meet individual patient or health professional anatomical features. The device is subject to this part and other requirements of this chapter and the act; the device is not exempt under this paragraph. (However, see paragraph (d)(3) (i) and (ii) of this section. Once the safety and effectiveness of the device are established, generally by means of premarket approval, the individual customizing of the device to meet patient or health professional needs will not render it again an investigational device subject to this part if the requirements of paragraph (d)(1) of this section are met.)

(iv) Fabrication of a device (for which insufficient information exists to determine whether the device is safe and effective) to meet unusual needs of patient: A health professional wants to order a device fabricated, or to fabricate a device, to meet the special needs of a patient who has unusual anatomical features; the device represents a new concept. The patient's special needs are such that the need for such a device is unlikely to recur, and these needs cannot be met by generally available devices or the devices described in paragraph (d)(3) (i) and (ii) of this section. The device shall meet the requirements of paragraph (d)(1) of this section.

(*a*) If the health professional informs the patient that the device represents a novel concept and is being specially fabricated to meet the patient's needs, the device is exempt from this part and section 514 (performance standards) and 515 (premarket approval) of the act if it is for use involving a single patient. It is subject to other requirements of this chapter and the act.

(*b*) If any health professional wishes to order such a device to meet similar special needs of any subsequent patient(s), the device is subject to the

ing on:

(1) The importance of the diagnostic or therapeutic uses of the device (i.e., whether a device is vital or nonvital), and

(2) The degree of risk presented by the device to the subjects participating in the study (i.e., substantial risk or low risk).

an investigational device subject to this part if the requirements of paragraph (d)(1) of this section are met.

(ii) Fabrication of a device (for which sufficient information exists to determine that the device is safe and effective) to meet individual needs of a patient or health professional: A manufacturer fabricates devices for health

from this part and section 514 (performance standards) and 515 (premarket approval) of the act if it is for use involving a single patient. It is subject to other requirements of this chapter and the act.

(*b*) If any health professional wishes to order such a device to meet similar special needs of any subsequent patient(s), the device is subject to the

requirements of this part, this chapter, and the act, unless the device involves application of such commonly recognized principles that its first use was sufficient to establish its safety and effectiveness, in which case the regulations applicable to the device are described in paragraph (d)(3)(ii) of this section.

(v) Fabrication of a device (for which insufficient information exists to determine whether the device is safe and effective) to meet unusual needs of health professional: A health professional wants to order a device fabricated, or to fabricate a device, to meet the special needs of the health professional in the course of his or her practice; the device represents a new concept. The special needs must relate to unusual anatomical features of the health professional (e.g., disability) or special needs of his or her practice that are not shared by other health professionals of the same specialty. The special needs requiring use of the device described in this clause must be the needs of the health professional rather than those of any particular patient. The special needs must be incapable of being met by generally available devices or the devices described in paragraph (d)(3) (i) and (ii) of this section. If the requirements of paragraph (d)(1) of this section are met and the device is for use only by the health professional who ordered it, it is exempt from this part and section 514 (performance standards) and 515 (premarket approval) of the act. It is subject to other requirements of this chapter and the act. If any other health professional wishes to order such a device, the rules in paragraph (d)(3)(iv)(b) of this section apply.

(e) *Studies by sole sponsor-investigator.* Sections 812.21(b)(8) (ii) and (iii), 812.46 (a) and (b), and 812.47 shall not apply to an investigational study that involves a sponsor-investigator who is the only investigator.

§ 812.3 Definitions.

(a) "Act" means the Federal Food, Drug, and Cosmetic Act, (sections 201-902, 52 Stat. 1040 et seq., as amended (21 U.S.C. 301-392)).

(b) "Institution" means a person, other than an individual, who engages in the conduct of research on human subjects or in the delivery of medical services to patients as a primary activity or as an adjunct to providing residential or custodial care to humans. The term includes a hospital, retirement home, prison, academic establishment, or device manufacturer. "Facility" as used in section 520(g) of the act is synonymous with the term "institution" for purposes of this part.

(c) "Institutionalized subject" means:

(1) A human subject who is voluntarily confined for a period of more than 24 continuous hours on the premises of, and in the care of, an institution (e.g., a hospital in-patient, or a resident in a retirement home), whether or not that institution is a sponsor of the investigational study; or

(2) A human subject who is involuntarily confined for any period of time in a penal institution (e.g., jail, workhouse, house of detention, or prison), or other institution (e.g., a hospital) by virtue of a sentence under a criminal or civil statute, or awaiting arraignment, commitment, trial or sentencing under such a statute, or by virtue of statutes or commitment procedures which provide alternatives to criminal prosecution or incarceration in a penal facility.

(d) An "institutional review committee" means any board, committee, or other group formally designated by institution for the purposes of reviewing clinical investigations or other types of biomedical research involving humans as subjects, approving the initiation of such investigations or research, overseeing the conduct of such investigations or research, and/or terminating or suspending such investigations or research, when necessary for the protection of subjects. The term has the same meaning as "institutional review board" in other Department regulations.

(e) "Investigational device" means a device that is used in an investigational study involving human subjects, where the purpose of the study is to determine whether the device is safe and/or effective.

(f) "Investigational plan" means a plan or protocol for using an investigational device in an investigational study where such plan or protocol meets the requirements of § 812.25.

(g) "Investigational study" means a study involving human subjects when the study is for the purpose of determining whether a device is safe and/or effective. An investigational study is considered a clinical investigation for purposes of Part 52 of this chapter.

(h) "Investigator" means an individual who actually conducts an investigational study, i.e., under whose immediate direction the investigational device is administered or dispensed to, or used involving, a subject.

(i) "Monitor," when used as a noun, means a designated individual selected by a sponsor or contract research organization to oversee the progress of an investigational study. The monitor may be a full-time employee of a sponsor or contract research organization or a consultant to the sponsor or contract research organization. "Monitor," when used as a verb, means the act of overseeing the progess of an investigational study in accordance with § 52.29 of this chapter.

(j) "Person" includes an individual, partnership, corporation, association, scientific or academic establishment, government agency or organizational unit thereof, and any other legal entity.

(k) "Sponsor" means a person who initiates a clinical investigation, but who does not actually conduct the investigation, i.e., the investigational device is administered or dispensed to or used involving a subject under the immediate direction of another individual. A person other than an individual (e.g., corporation or government agency) that uses one or more of its own employees to conduct a clinical investigation it has initiated is considered to be a sponsor (not a sponsor-investigator), and the employees are considered to be investigators.

(l) "Sponsor-investigator" means an individual who both initiates and actually conducts, alone or with others, an investigational study, i.e., under whose immediate direction the investigational device is administered or dispensed to, or used involving, a subject. The term does not include any person other than an individual, e.g., corporation or agency. The obligations or a sponsor-investigator under this part include those of an investigator.

(m) "Subject" means an individual who is or becomes a participant in an investigational study, either as a recipient of the investigational device or as a control. A subject may be either a human being in normal health or a patient to whom the investigational device might offer therapeutic benefit or as to whom it might provide diagnostic information.

(n) "Substantial risk" is a risk that may result in death or may produce morbidity (including disfigurement, permanent injury, or interference with the capacity to continue employment), require operation or reoperation, require extension of hospitalization (beyond that expected for the condition being treated), require rehospitalization, or cause increased invalidism; or, at the least, produce moderate personal discomfort and the need for extensive outpatient medical care.

(o) "Low risk" means a risk other than a substantial risk. It includes a situation in which no risk is presented, i.e., there is no possibility of injury to a subject's health or his or her rights.

(p) "Transitional period" applies only to those devices (other than devices that were regarded as new drugs or antibiotic drugs) which (1) were either in commercial distribution before May 28, 1976, or are judged by the Food and Drug Administration to be substantially equivalent to a device in commerical distribution before that date, and (2) are classified in class III under section 513(d) of the act. The transitional period for a particular device extends from May 28, 1976, to either (i) the last day of the 30th calendar month after the date the classi-

ment nome, prison, academic establishment, or device manufacturer. "Facility" as used in section 520(g) of the act is synonymous with the term "institution" for purposes of this part.

(c) "Institutionalized subject" means:

(1) A human subject who is voluntarily confined for a period of more

sor or contract research organization or a consultant to the sponsor or contract research organization. "Monitor," when used as a verb, means the act of overseeing the progess of an investigational study in accordance with § 52.29 of this chapter.

(j) "Person" includes an individual, partnership, corporation, association,

the Food and Drug Administration to be substantially equivalent to a device in commerical distribution before that date, and (2) are classified in class III under section 513(d) of the act. The transitional period for a particular device extends from May 28, 1976, to either (i) the last day of the 30th calendar month after the date the classi-

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fication of that device into class III becomes effective, or (ii) the 90th day after the date a regulation requiring the submission of a premarket approval application with respect to that device is promulgated, whichever occurs later.

(q) "Vital investigational device" means a device intended to support or sustain life or intended for surgical implant into the body (or a diagnostic device, e.g., an in vitro diagnostic product, which provides data which might reasonably be considered life supporting or vital to the care of the subject), or a device whose failure could result in permanent injury to the subject.

(r) "Nonvital investigational device" refers to any device other than a vital investigational device.

§ 812.5 General qualifications for an exemption.

A shipment of an investigational device is exempt from any or all of the otherwise applicable requirements of the act enumerated in § 812.1(c) if all of the following conditions are met:

(a) The label of the device bears the following: The name and place of business of the manufacturer, packer, or distributor in accordance with § 801.1 of this chapter; the quantity of contents; and the following statement (or, where appropriate, a statement prescribed in § 809.10(c) of this subchapter for an in vitro diagnostic product): "Caution—Investigational device. Limited by Federal (or United States) law to investigational use."

(b) The labeling of the device is not false or misleading in any particular, does not represent that the device is safe and/or effective for the purpose(s) for which it is being investigated, and describes all relevant hazards, contraindications, adverse effects, interfering substances or devices, and precautions suggested by prior investigations and experience with the investigational device or any related device.

(c) If the shipment is for an investigational study involving human subjects:

(1) An application for investigational device exemption (or notification) covering that shipment was submitted by the sponsor under Subpart B of this part.

(2) The requisite time has elapsed following the date of receipt of the application (or notification) by the Food and Drug Administration to permit the investigational study to begin under §§ 812.20(c) or 812.30(b), or the Commissioner has approved the application where required by § 812.30 (a)(2).

(3) The Commissioner has not disapproved the application (or notification) or withdrawn the exemption.

(4) Each shipment of the device is made in accordance with the commitments in the application (or notification) and any conditions imposed in the Commissioner's approval pursuant to § 812.30.

(5) The sponsor has complied with the requirements of this part and Part 52 of this chapter; any institutional review committee that is to review and approve the investigational study for which shipment is made has complied with Food and Drug Administration regulations regarding standards for such committees; and the investigator(s) to whom the shipment is to be made has complied with Food and Drug Administration regulations regarding the obligations of clinical investigators.

(d) If the shipment is intended solely for tests in laboratory animals, or for other tests that do not involve human subjects, the requirements of Subpart H of this part and applicable requirements in Part 58 of this chapter have been met.

(e) If the shipment is to be imported into or exported from the United States, the requirements of § 812.19 have been met.

§ 812.10 Petitions for waiver of requirements.

(a) Any person subject to any requirement under this part may petition the Commissioner for a waiver of such requirement. Such a petition shall be submitted in accordance with § 10.30 of this chapter and shall set forth the basis for the petitioner's belief that compliance with the requirement is not necessary to achieve the objectives of this part and, where appropriate, any alternative means to achieve the objective of the requirement from which the waiver is sought.

(b) The Commissioner may, at the Commissioner's discretion, grant a petition for a waiver submitted under this section if he finds that compliance with the requirement from which the waiver is sought is not necessary to achieve the objectives of this part and, where appropriate, that the proposed alternative means will acheive the objective of the requirement from which the waiver is sought.

(c) The person who submits a petition under this section shall continue to be subject to the requirement from which the waiver is sought unless and until the Commissioner grants the petition.

§ 812.12 Information previously submitted.

Wherever this part requires the submission to the Food and Drug Administration of information or data that were previously submitted in accordance with this part or other parts of this chapter, the information or data need not be resubmitted but may be incorporated by reference.

§ 812.19 Requirements applicable to importers and exporters of investigational devices.

(a) Any person who imports or offers for importation into the United States an investigational device shall assure that all of the following requirements are met:

(1) The labeling of such device complies with § 812.5 (a) and (b).

(2) If the device is for an investigational study involving human subjects:

(i) The importer of such shipment is an agent in the United States of the foreign exporter or is the ultimate consignee, and the foreign exporter or the ultimate consignee has, before such shipment, completed and submitted to the Food and Drug Administration an application for an investigational device exemption in accordance with § 812.21 or, when permitted, a notification in accordance with § 812.20 and acts as the sponsor of the investigational study to assure compliance with applicable requirements of this chapter.

(ii) The requisite time has elapsed following the date of receipt of the notification or application by the Food and Drug Administration to permit the investigational study to begin under §§ 812.20(c) or 812.30(b), or the Commissioner has approved the application, where required by § 812.30(a)(2).

(iii) The Commissioner has not disapproved the application (or notification) or withdrawn the exemption

(b) (1) A device exported from the United States to a foreign country that does not comply with requirements of the Act shall not be deemed adulterated or misbranded if:

(i) The device conforms to the specifications of the foreign purchaser.

(ii) The device complies with the laws of the country to which it is being exported.

(iii) The label on the outside of the shipping package indicates that the device is intended for export.

(iv) The device is not sold or offered for sale in domestic commerce.

(v) The device complies with any applicable requirements of paragraph (b)(2) of this section.

(2) If the following requirements in addition to the requirements of paragraph (b)(1) of this section are met, any person may export from the United States for an investigational study involving human subjects a device that is subject to a performance standard in effect under section 514 of the act and that does not comply with such standard; or that is required to have in effect an approved application for premarket approval under section 515 of the act, and that is not currently subject to a transitional period, and that does not have in effect an approved application; or that is subject to an exemption under this part from

under §§ 812.20(c) or 812.30(b), or the Commissioner has approved the application where required by § 812.30 (a)(2).

(3) The Commissioner has not disapproved the application (or notification) or withdrawn the exemption.

(4) Each shipment of the device is made in accordance with the commit-

tees.

Wherever this part requires the submission to the Food and Drug Administration of information or data that were previously submitted in accordance with this part or other parts of this chapter, the information or data need not be resubmitted but may be incorporated by reference.

the act and that does not comply with such standard; or that is required to have in effect an approved application for premarket approval under section 515 of the act, and that is not currently subject to a transitional period, and that does not have in effect an approved application; or that is subject to an exemption under this part from

sections 514 or 515 of the act; or that is subject to a banned device regulation under section 516 of the act:

(i) The exporter or any other person obtains documentation from the government of the foreign country that the export of the device to that country is approved by such government based upon adequate information about the device.

(ii) The exporter or other person submits to the Bureau of Medical Devices, Document Control Center (HFK-20), Food and Drug Administration, 8757 Georgia Avenue, Silver Spring, Md. 20910, a copy of this documentation, an explanation of why the proposed export of the device is not contrary to public health and safety, and a request for a determination that the export is not contrary to public health and safety.

(iii) The Commissioner has determined that the export of the device to the foreign country is not contrary to the public health and safety and has notified the exporter or other person of this determination.

(3) The Commissioner may by order disapprove the export of the device under this section if he determines that such export is contrary to the public health and safety. Such an order may provide that export will be permitted if there is compliance with this part.

Subpart B—Notifications and Applications for Exemption for Investigational Studies Involving Human Subjects

§ 812.20 Notification.

(a) *When submitted.* (1) Except as provided in § 812.21(a) (ii) and (iii), a notification shall be submitted when:

(i) A vital investigational device is to be used in an investigational study that presents low risk to human subjects, or

(ii) A nonvital investigational device is to be used in an investigational study.

(2) The sponsor of a study described in paragraph (a)(1) of this section shall submit to the Food and Drug Administration three copies of a completed "Notification of Intent to Investigate a Device" and of all materials required by paragraph (b) of this section to accompany such a notification, bound and contained in volumes of reasonable size, by registered mail or hand delivery to the Bureau of Medical Devices, Document Control Center (HFK-20), Food and Drug Administration, 8757 Georgia Avenue, Silver Spring, Md. 20910. The outside wrapper shall be labeled "Notification of Intent to Commence Testing an Investigational Device." Any subsequent reports and correspondence concerning an application shall be submitted in triplicate by registered mail or hand delivery to this address.

(b) *Contents.* A notification shall include the name and address of the sponsor, the name and description of the investigational device; a summary of the investigational plan; location(s) of the study; an agreement to comply with Subpart C of this part and Part 52 of this chapter; written procedures established by the sponsor for monitoring the investigational study under Part 52 of this chapter (unless the study involves a sponsor-investigator who is the only investigator); institutional review committee(s) approval of the study in accordance with § 52.25 of this chapter and agreement to comply with Food and Drug Administration regulations on institutional review committees; a statement from each institutional review committee involved, signed by the chairman, assessing whether the device is vital or nonvital and the degree of risk to which the subjects will be exposed; and, in accordance with § 812.21(b)(7), the name(s) of investigators and the agreement of each investigator to comply with Food and Drug Administration regulations regarding obligations of clinical investigators. A notification shall be signed by an authorized representative of the sponsor.

(c) *FDA review.* After receipt of a notification, the Food and Drug Administration will send the sponsor a letter as soon as possible informing the sponsor of the date of receipt.

(2) The procedures in §§ 812.30 through 812.35 for approval or disapproval of an application for an investigational device exemption and for withdrawal of an exemption shall apply to a notification, except as provided in paragraph (d) of this section.

(d) *When study may begin.* Where the sponsor states that a nonvital investigational device is to be used in an investigational study that presents low risk to human subjects, and the Food and Drug Administration's letter informing the sponsor of receipt of the notification does not also inform the sponsor that an application is required rather than a notification, the exemption takes effect and the study may begin after the sponsor's receipt of the letter. Otherwise the exemption does not take effect and the study shall not begin until the notification is approved or deemed approved under § 812.30.

(e) *Other requirements.* Requirements in this subchapter (other than § 812.21) applicable to an application for investigational device exemption shall apply to a notification. Requirements in this subchapter for sponsors, investigators, and institutional review of clinical investigations apply to studies under an investigational devices exemption obtained under this section by a notification.

§ 812.21 Application.

(a) *When submitted.* (1) An application shall be submitted when:

(i) A vital investigational device is to be used in an investigational study that presents substantial risk to human subjects;

(ii) A sponsor of a study described in § 812.20(a) elects to submit an application instead of a notification; or

(iii) The Food and Drug Administration notifies the sponsor under § 812.20(d) that an application is required.

(2) The sponsor of an investigational study described in paragraph (a)(1) of this section shall submit to the Food and Drug Administration a completed "Application for an Investigational Device Exemption" that has been signed by an authorized representative of the sponsor. Three copies of the application and any material required to accompany the application, bound and contained in volumes of reasonable size, shall be submitted by registered mail or hand delivery to the Bureau of Medical Devices, Document Control Center (HFK-20), Food and Drug Administration, 8757 Georgia Avenue, Silver Spring, Md. 20910. Any subsequent reports, any correspondence concerning an application and any supplemental application submitted under § 812.39 also shall be submitted in triplicate by registered mail or hand delivery to this address. The outside wrapper of any application or supplemental application shall include the statement "Application or Supplemental Application for Investigation Device Exemption" and the outside wrapper of any reports or correspondence shall include the statement "Regarding an Investigational Device Exemption."

(b) *Contents.* An application for an investigational device exemption shall include: the sponsor's name, address, telephone number, the name of the sponsor's representative to whom communications should be sent, the location(s) where the study will be conducted, and the following information:

(1) The best available descriptive name of the device and a brief statement of its intended use(s) and how it is to be used.

(2) A description of the important components, ingredients, and properties and a description of the principle(s) of operation of the device and any anticipated changes in the device that may occur in the course of the study, in enough detail so that a scientist or physician familiar with the general type of device, but not necessarily an expert with regard to the specific device, can make a knowledgeable judgment about the anticipated safety and effectiveness of the device in the proposed investigational study.

(3) A description of those methods, facilities, and controls used for the manufacture, processing, packing, storage, and, where appropriate, in-

tion; 8757 Georgia Avenue, Silver Spring, Md. 20910. The outside wrapper shall be labeled "Notification of Intent to Commence Testing an Investigational Device." Any subsequent reports and correspondence concerning an application shall be submitted in triplicate by registered mail or hand delivery to this address.

investigators, and institutional review of clinical investigations apply to studies under an investigational devices exemption obtained under this section by a notification.

§ 812.21 Application.

(a) When submitted. (1) An application shall be submitted when:

(i) A vital investigational device is to be used in an investigational study that presents substantial risk to human subjects;

(ii) A sponsor of a study described in § 812.20(a) elects to submit an application instead of a notification; or

(iii) The Food and Drug Administration notifies the sponsor under § 812.20(d) that an application is required.

(2) The sponsor of an investigational study described in paragraph (a)(1) of this section shall submit to the Food and Drug Administration a completed "Application for an Investigational Device Exemption" that has been signed by an authorized representative of the sponsor. Three copies of the application and any material required to accompany the application, bound and contained in volumes of reasonable size, shall be submitted by registered mail or hand delivery to the Bureau of Medical Devices, Document Control Center (HFK-20), Food and Drug Administration, 8757 Georgia Avenue, Silver Spring, Md. 20910. Any subsequent reports, any correspondence concerning an application and any supplemental application submitted under § 812.39 also shall be submitted in triplicate by registered mail or hand delivery to this address. The outside wrapper of any application or supplemental application shall include the statement "Application or Supplemental Application for Investigation Device Exemption" and the outside wrapper of any reports or correspondence shall include the statement "Regarding an Investigational Device Exemption."

(b) Contents. An application for an investigational device exemption shall include: the sponsor's name, address, telephone number, the name of the sponsor's representative to whom communications should be sent, the location(s) where the study will be conducted, and the following information:

(1) The best available descriptive name of the device and a brief statement of its intended use(s) and how it is to be used.

(2) A description of the important components, ingredients, and properties and a description of the principle(s) of operation of the device and any anticipated changes in the device that may occur in the course of the study, in enough detail so that a scientist or physician familiar with the general type of device, but not necessarily an expert with regard to the specific device, can make a knowledgeable judgment about the anticipated safety and effectiveness of the device in the proposed investigational study.

(3) A description of those methods, facilities, and controls used for the manufacture, processing, packing, storage, and, where appropriate, in-

stallation of the device, in enough detail so that a person generally familiar with the manufacture of the general type of device can make a knowledgeable judgment about the safety and effectiveness of the device in the proposed investigational study.

(4) (i) A statement by the sponsor which tells the location of each institutional review committee that is to review a portion of the study (see § 812.42) and indicates that each committee has received a copy of an investigational plan (that meets the requirements of § 312.25), a report of prior investigations of the device (that meets the requirements of § 812.27), and any separate protocols or other materials required by such committee, and a statement that the committee(s) has approved the study.

(ii) If the study or any portion of the study is not to be reviewed by an institutional review committee at one or more locations where the study is to be conducted, a request for waiver of the institutional review requirement of § 812.42 that includes the sponsor's explanation (and supporting data) of why a committee is not necessary either for protecting the subjects or for ensuring the reliability of the scientific data.

(iii) A copy for the Food and Drug Administration of the investigational plan (that meets the requirements of § 812.25), the report of prior investigations of the device (that meets the requirements of § 812.27), and any separate protocols or other materials submitted to an institutional review committee.

(5) A statement from every institutional review committee involved in the study, signed by the chairman, that the committee has approved the investigational plan and has reviewed the report of prior investigations of the device, that the committee will review the study, in accordance with Food and Drug Administration regulations on institutional review, for its duration periodically at intervals appropriate to the degree of risk but not to exceed 1 year, and that it will review reports of unexpected adverse effects on a timely basis for the purpose of determining whether the study should be continued.

(6) A copy of all forms and informational materials to be given to human subjects including those to be used to obtain informed consent as required by Subpart F of this part. (The copy may be appended to the investigational plan.)

(7) A copy of the agreement(s), which includes a statement of the investigator's curriculum vitae, to comply with Food and Drug Administration regulations regarding the obligations of investigators, signed by each investigator who will be taking part in the investigational study as required by § 812.43(b).

(8)(i) A copy of all informational material, including labels and other labeling. Such informational material shall meet the requirements of § 812.5.

(ii) Except where the application is submitted by a sponsor-investigator who is the only investigator, a description of the scientific training and experience that the sponsor considers appropriate to qualify individuals as suitable experts to investigate the safety and effectiveness of the device, in view of the investigational plan, the report of prior investigations of the device, and what is known about the device.

(iii) Except where the application is submitted by a sponsor-investigator who is the only investigator, written procedures established by the sponsor for monitoring the investigational study in compliance with Part 52 of this chapter.

(iv) The name and a summary of the training and experience of the monitor(s) of the study under §§ 52.28 and 52.29 of this chapter.

(9) A statement to the best of the sponsor's knowledge as to whether any institutional review committee has ever disapproved or terminated any investigational study of the device and the reasons for such action.

(10) A statement that the sponsor will comply with the requirements applicable to sponsors under this chapter.

(11) A statement by a sponsor notifying the Food and Drug Administration of his intent, if any, to charge investigators and subjects for the device. (The Food and Drug Administration's failure to object to such a statement in an application is not authorization to begin commercial distribution of the device.)

(12) A statement by the sponsor of the reasons for requesting a waiver of the requirement that a study shall not begin before the expiration of 30 days after the Food and Drug Administration has received an application meeting the requirements of this subpart, if such a waiver is requested.

(13) An environmental analysis report meeting the requirements of Part 25 of this chapter when requested by the Food and Drug Administration after receipt of an application under this section.

(14) Any other information relevant to review of the applications, required by the Food and Drug Administration to be submitted.

(c) The sponsor may refuse to provide any information required by the Food and Drug Administration under paragraph (b)(14) of this section and treat the request as a disapproval of the application for purposes of requesting a hearing under § 812.30. In the event a sponsor fails to respond to a request for information within the time prescribed in the request, the Food and Drug Administration may treat the application as withdrawn and so notify the sponsor.

§ 812.25 Investigational plan.

(a) The investigational plan for the investigational study of a device shall include the following:

(1) A statement of the intended use of the device;

(2) A general outline of the plan and any anticipated or foreseeable changes or variations in the plan that may be made based on experience gained in the study;

(3) A statement describing the objectives of the investigational study;

(4) A justification for commencing the study, taking into account the report of prior investigations of the device;

(5) The expected duration of the investigational study;

(6) Identification of the investigator or investigators, the facilities where the study will occur, and any institutional review committees that will supervise the study;

(7) The patient population in which the device will be used (in terms of age, sex, and condition) and the size of such population;

(8) A justification for using such patient population and of the size of such population;

(9) A description of records to be maintained, and the reports to be made, by the investigator(s) and the sponsor to assure compliance with the plan and enable the progress of the investigation and the safety and effectiveness of the device to be reviewed by the sponsor, any institutional review committee, and the Food and Drug Administration;

(10) The plan for obtaining informed consent from subjects, including copies of all forms and informational materials to be provided to subjects; and

(11) A description of the important components, ingredients, properties and principle(s) of operation of the device in accordance with § 812.21(b)(2) and of any anticipated changes in the device that may occur in the course of the study.

(b) The procedures and conditions in the investigational plan may vary depending on (1) the scope and duration of the investigational study, (2) the number of human subjects who are to be involved in the study, (3) the need to permit changes to be made in the device during the study conducted in accordance with the plan, and (4) the purpose of the study, e.g., whether the study is designed for the purpose of developing data to obtain approval for the commercial distribution of the device.

(c) Where an investigational study is for the purpose of developing data to obtain premarket approval of the

(7) A copy of the agreement(s), which includes a statement of the investigator's curriculum vitae, to comply with Food and Drug Administration regulations regarding the obligations of investigators, signed by each investigator who will be taking part in the investigational study as required by § 812.43(b).

vide any information required by the Food and Drug Administration under paragraph (b)(14) of this section and treat the request as a disapproval of the application for purposes of requesting a hearing under § 812.30. In the event a sponsor fails to respond to a request for information within the time prescribed in the request, the

accordance with the plan, and (4) the purpose of the study, e.g., whether the study is designed for the purpose of developing data to obtain approval for the commercial distribution of the device.

(c) Where an investigational study is for the purpose of developing data to obtain premarket approval of the

device, the Food and Drug Administration will not ordinarily regard an investigational plan as providing data that will support an application for such approval unless it provides for more than one independent qualified investigator to study an adequate number of subjects in accordance with this chapter.

(d) Any summary of an investigational plan required under §§ 312.20 or 812.21 shall include an adequate and accurate summary of each of the elements of an investigational plan under paragraph (a) of this section.

(e) The investigational plan may provide for additional animal tests to be made during the course of the study.

§ 812.27 Report of prior investigations of a device.

(a) The report of prior investigations of a device, to be submitted to an institutional review committee and to the Food and Drug Administration, shall include information concerning prior investigations of the device that is adequate to justify the clinical testing involving human subjects as proposed in the investigational plan under § 812.25.

(b) The report of prior investigations of a device shall include:

(1) A bibliography of any publications relevant to the investigational study and copies of the significant publications both adverse and supporting.

(2) Any other unpublished information available to the sponsor, both supporting and adverse, information relating to nonclinical investigations of the device, including appropriate tests in animals and tests in vitro, and prior clinical investigations of the device or clinical experience with the device from commercial marketing, whether in the United States or in foreign countries, in sufficient detail so that a scientist or physician familiar with the general type of device, although not necessarily an expert with regard to the specific device, could make a knowledgeable judgment about the safety and efffectiveness of the device in the proposed investigational study.

(3) If information on nonclinical investigations is provided and the device is subject to the good laboratory practice regulations in Part 58 of this chapter, either a statement that all nonclinical investigations have been conducted in compliance with such regulations or, if such investigations have not been conducted in compliance with such regulations, a detailed description of all differences between the practices used in the investigations and those required in the regulations.

(c) Prior investigations of a device shall not be considered adequate to justify an investigational study involving human subjects unless the conditions (except for the subjects involved) of the prior investigations of the device are comparable to the conditions of the proposed investigational study.

(d) Except where tests on laboratory animals would be unnecessary, e.g., where in the judgment of the institutional review committee and the Food and Drug Administration there have been adequate in vitro tests or there is ample literature concerning prior clinical investigations or clinical experience, prior investigation of a device will be considered adequate to justify the investigational use of the device in human subjects only if:

(1) The device has been tested in laboratory animals and these tests show that it is reasonably safe to begin an investigational study involving human subjects; and

(2) The report of prior investigations of the device provides sufficient details concerning such investigations to permit scientific evaluation.

(e) Where the device consists of several components or ingredients that may have a significant effect on the safety or effectiveness of the device, and information concerning such components or ingredients is needed to justify the investigational use of the device in human subjects, the report of prior investigations of a device shall include a summary of the same type of information relating to these components and ingredients required for the device by paragraph (b) (1) and (2) of this section.

§ 812.30 Food and Drug Administration review of and action on an application.

(a) Upon receipt of an application for an investigational device exemption submitted in accordance with this subpart, the Food and Drug Administration will notify the sponsor of the date of such receipt and inform the sponsor that the investigational study may not begin:

(1) Until 30 days after the date of receipt of the application by the Food and Drug Administration, unless the agency has decided to waive the 30-day time requirement and so informs the sponsor; or

(2) In the case of an application for an exemption from the banned device provisions of sections 516 of the act, until the Food and Drug Administration approves the application under this paragraph and notifies the sponsor of the approval.

(b) An application for an investigational device exemption (other than an application described in paragraph (a)(2) of this section), shall be deemed to be approved on the 30th day after receipt of the application by the Food and Drug Administration unless, on or before such day, the Commissioner finds that the application does not meet the requirements of this part and other provisions of this chapter concerning clinical investigations (e.g., Part 52 of this chapter) and by order disapproves the application for any of the grounds in paragraph (c) of this section and states his reasons therefor, or finds the application deficient and requests additional information, or suggests revisions. If the Commissioner requests additional information or suggests revisions, the sponsor may treat the application as disapproved for purposes of requesting a regulatory hearing under Part 16 of this chapter. The Commissioner may approve an application with modifications, e.g., subject to conditions.

(c) The Commissioner may by order disapprove an application if he makes any of the following findings:

(1) The application contains an untrue statement of a material fact or omits material information required by §§ 812.20 or 812.21.

(2) The report of prior investigations of the device is inadequate to support a conclusion that it is reasonably safe to begin or continue the proposed investigational study.

(3) There is reason to believe that the device may be unsafe or ineffective when used for the purpose or in the manner for which it is to be investigated.

(4) The investigational plan described in the application is not a reasonable plan, in whole or in part, for a scientific investigation to determine whether the device is safe or effective.

(5) The methods, facilities, and controls used for the manufacturing, processing, packing, storage, and, where appropriate, installation of the device do not adequately ensure the safety and effectiveness of the device.

(6) The sponsor's proposed use of the device is not intended solely for an investigational study because it is being or is to be sold or otherwise commercially distributed in a manner not justified by the requirements of the investigational study and not permitted by this part or Part 52 of this chapter.

(7) There has not been compliance with the requirements prescribed in this part or applicable requirements in Part 52 or other regulations in this chapter regarding responsibilities of sponsors, clinical investigators, and institutional review boards, respectively.

(8) The application contained a nonclinical laboratory study of a device that is subject to the good laboratory practice regulations in Part 58 of this chapter, and the study was not conducted in compliance with such regulations, or any differences between the practices and in conducting the study and those required in the regulations were not described in detail.

(9) The proposed investigational study subjects human subjects to undue risks. In assessing risks, the

regulations or, if such investigations have not been conducted in compliance with such regulations, a detailed description of all differences between the practices used in the investigations and those required in the regulations.

(c) Prior investigations of a device shall not be considered adequate to justify an investigational study involving human subjects unless the conditions (except for the subjects involved) of the prior investigations of the device are comparable to the conditions of the proposed investigational study.

(d) Except where tests on laboratory animals would be unnecessary, e.g., where in the judgment of the institutional review committee and the Food and Drug Administration there have been adequate in vitro tests or there is ample literature concerning prior clinical investigations or clinical experience, prior investigation of a device will be considered adequate to justify the investigational use of the device in human subjects only if:

(1) The device has been tested in laboratory animals and these tests show that it is reasonably safe to begin an investigational study involving human subjects; and

(2) The report of prior investigations of the device provides sufficient details concerning such investigations to permit scientific evaluation.

(e) Where the device consists of several components or ingredients that may have a significant effect on the safety or effectiveness of the device, and information concerning such components or ingredients is needed to justify the investigational use of the device in human subjects, the report of prior investigations of a device shall include a summary of the same type of information relating to these components and ingredients required for the device by paragraph (b) (1) and (2) of this section.

§ 812.30 Food and Drug Administration review of and action on an application.

(a) Upon receipt of an application for an investigational device exemption submitted in accordance with this subpart, the Food and Drug Administration will notify the sponsor of the date of such receipt and inform the sponsor that the investigational study may not begin:

(1) Until 30 days after the date of receipt of the application by the Food and Drug Administration, unless the agency has decided to waive the 30-day time requirement and so informs the sponsor; or

(2) In the case of an application for an exemption from the banned device provisions of sections 516 of the act, until the Food and Drug Administration approves the application under this paragraph and notifies the sponsor of the approval.

(b) An application for an investigational device exemption (other than an application described in paragraph (a)(2) of this section), shall be deemed to be approved on the 30th day after receipt of the application by the Food and Drug Administration unless, on or before such day, the Commissioner finds that the application does not meet the requirements of this part and other provisions of this chapter concerning clinical investigations (e.g., Part 52 of this chapter) and by order disapproves the application for any of the grounds in paragraph (c) of this section and states his reasons therefor, or finds the application deficient and requests additional information, or suggests revisions. If the Commissioner requests additional information or suggests revisions, the sponsor may treat the application as disapproved for purposes of requesting a regulatory hearing under Part 16 of this chapter. The Commissioner may approve an application with modifications, e.g., subject to conditions.

(c) The Commissioner may by order disapprove an application if he makes any of the following findings:

(1) The application contains an untrue statement of a material fact or omits material information required by §§ 812.20 or 812.21.

(2) The report of prior investigations of the device is inadequate to support a conclusion that it is reasonably safe to begin or continue the proposed investigational study.

(3) There is reason to believe that the device may be unsafe or ineffective when used for the purpose or in the manner for which it is to be investigated.

(4) The investigational plan described in the application is not a reasonable plan, in whole or in part, for a scientific investigation to determine whether the device is safe or effective.

(5) The methods, facilities, and controls used for the manufacturing, processing, packing, storage, and, where appropriate, installation of the device do not adequately ensure the safety and effectiveness of the device.

(6) The sponsor's proposed use of the device is not intended solely for an investigational study because it is being or is to be sold or otherwise commercially distributed in a manner not justified by the requirements of the investigational study and not permitted by this part or Part 52 of this chapter.

(7) There has not been compliance with the requirements prescribed in this part or applicable requirements in Part 52 or other regulations in this chapter regarding responsibilities of sponsors, clinical investigators, and institutional review boards, respectively.

(8) The application contained a nonclinical laboratory study of a device that is subject to the good laboratory practice regulations in Part 58 of this chapter, and the study was not conducted in compliance with such regulations, or any differences between the practices and in conducting the study and those required in the regulations were not described in detail.

(9) The proposed investigational study subjects human subjects to undue risks. In assessing risks, the

Commissioner shall consider, among other things, the factors enumerated in § 812.35(a)(11).

(d) The Commissioner shall notify the sponsor of an approval of an application with modifications, of an approval under paragraph (a)(2) of this section, or of a disapproval. The notification shall contain the order of approval or disapproval and a complete statement of the reasons for the order. A notification of approval with modifications or disapproval shall advise the sponsor that the sponsor has recourse to an opportunity for a regulatory hearing under Part 16 of this chapter.

(e) The Commissioner may, in the Commissioner's discretion, decide not to disapprove an application for which there are grounds for disapproval if the facts do not lead the Commissioner to conclude that the risks outweigh the benefits to subjects, considering the factors enumerated in § 812.35(a)(11).

(f) The Commissioner shall make publicly available a summary of the information on the safety and effectiveness of a device that was submitted under this part and was the basis for an order under paragraph (a)(2) of this section approving an exemption from a banned device regulation or under paragraph (c) of this section disapproving an application. The summary shall be made publicly available, on request, upon issuance of the order and shall include information on any adverse effects of the device on health.

§ 182.35 Withdrawal of an exemption.

(a) The Commissioner may by order withdraw an exemption granted under this part, if he makes any of the following findings:

(1) The application for such exemption or any subsequent report contains an untrue statement of a material fact or omits material information required by this part (e.g., §§ 812.20, 812.21, or 812.39) or Part 52 of this chapter.

(2) The report of prior investigations of the device is inadequate to support a conclusion that it is reasonably safe to continue the investigational study.

(3) There is reason to believe that the device may be or is unsafe and/or ineffective when used for the purpose or in the manner for which it is investigated.

(4) The investigational plan described in the application or notification is not a reasonable plan, in whole or in part, for a scientific investigation to determine whether the device is safe and/or effective.

(5) The methods, facilities, and controls used for the manufacturing, processing, packing, storage, and, where appropriate, installation of the device do not adequately ensure its safety and effectiveness.

(6) The investigational study is not being conducted in accordance with the investigational plan submitted to the Food and Drug Administration or the institutional review committee; or any change in or deviation from the investigational plan was not approved as required by § 812.39.

(7) The sponsor's use of the investigational device is not intended solely for an investigational study, because it is being or is to be sold or otherwise commercially distributed in a manner not justified by the requirements of the investigational study and not permitted by this part or Part 52 of this chapter.

(8) The sponsor has unduly prolonged an investigational study without submitting an application for premarket approval of the device as required by § 812.46(d).

(9) The investigational study is not being conducted in compliance with the requirements of this part or applicable requirements of Parts 52, 54, or 56 of this chapter regarding responsibilities of sponsors, clinical investigators and institutional review boards, respectively.

(10) The application contained a nonclinical laboratory study of a device that is subject to the good laboratory practice regulations in Part 58 of this chapter, and the study was not conducted in compliance with such regulations, or any differences between the practices used in conducting the study and those required in the regulations were not described in detail.

(11) The proposed investigational study subjects human subjects to undue risks. In assessing risks, the Commissioner shall consider, among other things, whether:

(i) The risks to the subject are so outweighed by the sum of the potential benefits to the subject and the importance of the knowledge to be gained as to warrant a decision to allow the subject to accept these risks;

(ii) The rights and welfare of any such subject will be or have been adequately protected;

(iii) Legally effective informed consent will be or has been obtained by adequate and appropriate methods in accordance with the provisions of Subpart F of this part;

(iv) The conduct of the activity will be or has been reviewed at timely intervals by the institutional review committee, the sponsor, or both.

(12) The process of review or monitoring undertaken by the institutional review committee that is monitoring the study is inadequate.

(b) An order withdrawing an exemption shall include a complete statement of the reasons for the Commissioner's action. Such order shall be issued only after the sponsor has been afforded an opportunity for a regulatory hearing under Part 16 of this chapter, except that the order may be issued before providing an opportunity for such hearing if the Commissioner determines that the continuation of testing under the exemption concerning which the order is to be issued will result in an unreasonable risk to the public health or safety.

(c) The Commissioner may, in the Commissioner's discretion, decide not to withdraw an exemption for which there are grounds for withdrawal if the facts do not lead the Commissioner to conclude that the risks outweigh the benefits to subjects, considering the factors in paragraph (a)(11) of this section.

(d) An exemption that has been withdrawn under this section may be reinstated if the sponsor satisfies the Commissioner that the grounds for withdrawal no longer apply.

(e) The Commissioner shall prepare a summary of the information on the safety and effectiveness of a device that was submitted under this part and was the basis for an order under paragraph (a) of this section withdrawing an exemption that permitted an investigational study of the device. The summary shall be made publicly available, on request, upon issuance of the order and shall include information on any adverse effects on health of the device.

§ 812.38 Confidentiality of data and information in an application.

(a) [Reserved]

(b) The availability for public disclosure of all data and information in the Food and Drug Administration file concerning the application or notification shall be handled in accordance with the provisions established in § 314.14 of this chapter for the confidentiality of data and information in new drug applications.

(c) Notwithstanding the provisions of § 314.14 of this chapter, the Food and Drug Administration shall disclose upon request to an individual on whom an investigational device has been used a copy of any adverse reaction report relating to such individual as a result of such use.

§ 812.39 Supplemental applications and submissions concerning applications.

(a) Except as provided in paragraphs (b), (c), and (d) of this section, information contained in an application submitted under § 812.21 or notification submitted under § 812.20 may be updated by means of a report to the Food and Drug Administration under § 812.55.

(b)(1) Whenever the sponsor or any investigator participating in an investigational study wishes to implement a change in, or deviation from, the investigational plan submitted to the Food and Drug Administration or an institutional review committee that may affect the validity of the study or

to determine whether the device is safe and/or effective.

(5) The methods, facilities, and controls used for the manufacturing, processing, packing, storage, and, where appropriate, installation of the device do not adequately ensure its safety and effectiveness.

(6) The investigational study is not being conducted in accordance with the investigational plan submitted to the Food and Drug Administration or the institutional review committee; or any change in or deviation from the investigational plan was not approved as required by § 812.39.

(7) The sponsor's use of the investigational device is not intended solely for an investigational study, because it is being or is to be sold or otherwise commercially distributed in a manner not justified by the requirements of the investigational study and not permitted by this part or Part 52 of this chapter.

(8) The sponsor has unduly prolonged an investigational study without submitting an application for premarket approval of the device as required by § 812.46(d).

(9) The investigational study is not being conducted in compliance with the requirements of this part or applicable requirements of Parts 52, 54, or 56 of this chapter regarding responsibilities of sponsors, clinical investigators and institutional review boards, respectively.

(10) The application contained a nonclinical laboratory study of a device that is subject to the good laboratory practice regulations in Part 58 of this chapter, and the study was not conducted in compliance with such regulations, or any differences between the practices used in conducting the study and those required in the regulations were not described in detail.

(11) The proposed investigational study subjects human subjects to undue risks. In assessing risks, the Commissioner shall consider, among other things, whether:

(i) The risks to the subject are so outweighed by the sum of the potential benefits to the subject and the importance of the knowledge to be gained as to warrant a decision to allow the subject to accept these risks;

(ii) The rights and welfare of any such subject will be or have been adequately protected;

(iii) Legally effective informed consent will be or has been obtained by adequate and appropriate methods in accordance with the provisions of Subpart F of this part;

(iv) The conduct of the activity will be or has been reviewed at timely intervals by the institutional review committee, the sponsor, or both.

(12) The process of review or monitoring undertaken by the institutional review committee that is monitoring the study is inadequate.

(b) An order withdrawing an exemption shall include a complete statement of the reasons for the Commissioner's action. Such order shall be issued only after the sponsor has been afforded an opportunity for a regulatory hearing under Part 16 of this chapter, except that the order may be

Food and Drug Administration under § 812.55.

(b)(1) Whenever the sponsor or any investigator participating in an investigational study wishes to implement a change in, or deviation from, the investigational plan submitted to the Food and Drug Administration or an institutional review committee that may affect the validity of the study or

the rights or safety of the human subjects under the criteria in paragraph (b)(3) of this section, the investigator shall obtain the prior review and approval of any institutional review committee involved in the study. If the sponsor is amending an application rather than a notification, he shall also submit to the Food and Drug Administration a supplemental application describing the proposed change or deviation and justification therefor. Except as provided in paragraph (b)(2) of this section, the sponsor shall submit the supplemental application before the change or deviation is implemented, with a copy of the approval of the change or deviation by any institutional review committee evidenced by a statement from the chairman. The sponsor shall not permit the change or deviation to be implemented unless and until the supplemental application is approved or deemed approved by the Food and Drug Administration under § 812.30(b), except as described in paragraph (b)(2) of this section.

(2) When a change or deviation is necessary to eliminate or reduce an apparent immediate hazard to the safety of a human subject who is already participating in the investigational study, the investigator and the sponsor are not required to comply with the prior approval requirements of paragraph (b)(1) of this section. The investigator shall instead notify any institutional review committee of the change or deviation and the justification therefor as soon as possible but in no event later than 5 days after the change or deviation has been implemented. The sponsor shall instead notify the Food and Drug Administration as soon as possible but in no event later than 5 days after learning of the change or deviation.

(3) The following changes in, or deviations from, an investigational plan illustrate some of the situations in which prior review and approval are required under paragraph (a) of this section:

(i) A significant change in the administration of, or where appropriate, in the application or frequency of, or a change in the method of, administration or use of the investigational device.

(ii) A significant change in the number of subjects participating in the study at one time or cumulatively.

(iii) The utilization of subjects with medical conditions unrelated to, but possibly affecting, the scope or validity of the study, e.g., use of terminally ill patients in an investigation unrelated to the terminal illnesses.

(iv) The utilization of human subjects who require special consideration or protection and who are not listed specifically in the plan, e.g., children, pregnant women, or mentally disabled individuals.

(v) The administration of concomitant or concurrent therapy where it is likely that an interaction or interference with the investigational device might occur.

(c) The sponsor shall submit to the Food and Drug Administration the signed statements required under §§ 812.43(b) and 812.21(b)(5) for any additional investigators and institutional review committees who are added to an investigational study after submission of a notification under § 812.20 or an application for an investigational device exemption under § 812.21(b). Any such additional statement shall be submitted before an investigator may begin participation in the investigational study except that:

(1) The sponsor may request Food and Drug Administration approval to add additional investigators to the study by rapid communication techniques before submitting the signed statements.

(2) When there exists a life-threatening situation that necessitates the use of an investigational device, prior notification is not required.

(3) When a study is being conducted under a notification pursuant to § 812.20, prior notification is not required.

(d) The sponsor shall submit to the Food and Drug Administration any additional forms, or revisions in forms, or other informational materials to be provided to human subjects and any additional informational materials, or revisions in such informational materials, supplied to investigators, which had not previously been submitted to the Food and Drug Administration. The sponsor shall submit such forms or materials to the Food and Drug Administration at the same time that they are provided to investigators.

Subpart C—Sponsor Responsibilities in Investigational Studies Involving Human Subjects

§ 812.40 General.

The requirements of this subpart are applicable to sponsors of investigational studies, including sponsor-investigators, except as specifically provided otherwise in this chapter, e.g., § 812.2(e). Sponsors also are subject to other requirements under this part and Parts 52 and 58 of this chapter.

§ 812.42 Review of the investigational study by the Food and Drug Administration and the institutional review committee.

(a) Before any human subject is allowed, or requested formally to consent to, participation in the investigational study, the sponsor shall ensure the following:

(1) The requirements of § 52.25 of this chapter concerning assurance of institutional review are met, where institutional review is required under paragraphs (b) through (d) of this section.

(2) The sponsor has both submitted a notification or application for an investigational device exemption to the Food and Drug Administration and obtained an exemption from the Food and Drug Administration in accordance with §§ 812.20(d) or 812.30(b).

(b) Except as provided in paragraph (d) of this section, the Food and Drug Administration will not accept any notification or application for an investigational device exemption unless the investigational study has been reviewed and approved, and remains subject to continuing review, by an institutional review committee meeting the requirements of Food and Drug Administration regulations.

(c) Except as provided in paragraph (d) of this section, the Food and Drug Administration will not consider in support of an application for a research or marketing permit (as defined in § 52.3(b) of this chapter) any data or information that has been derived from an investigational study unless that study had been approved by, and was subject to initial and continuing review by an institutional review committee meeting the requirements of Food and Drug Administration regulations. The determination that an investigational study may not be considered in support of an application for a research or marketing permit does not, however, relieve the applicant for such a permit of any obligation under any other applicable regulation to submit the results of the investigation to the Food and Drug Administration.

(d) (1) Except as provided in paragraph (d)(2) of this section, the Food and Drug Administration may waive the requirement for institutional review on request of a sponsor of an application for an investigational device exemption (but not a notification), if the Commissioner determines that the requirement is not necessary either for protecting the subjects involved or for assuring the validity or reliability of the scientific data. Any applicant for an investigational device exemption or other research or marketing permit may include a request for waiver, with supporting information, in the application.

(2) The requirement for institutional review will not be waived in any of the following situations:

(i) When the clinical investigation involves institutionalized human subjects.

(ii) When the clinical investigation is conducted on the premises of an institution that has an institutional review committee meeting the requirements of Food and Drug Administration regulations.

(iii) When the Food and Drug Administration determines that the risks to the subjects justify such review.

possibly affecting, the scope or validity of the study, e.g., use of terminally ill patients in an investigation unrelated to the terminal illnesses.

(iv) The utilization of human subjects who require special consideration or protection and who are not listed specifically in the plan, e.g., children, pregnant women, or mentally disabled individuals.

committee.

(a) Before any human subject is allowed, or requested formally to consent to, participation in the investigational study, the sponsor shall ensure the following:

(1) The requirements of § 52.25 of this chapter concerning assurance of institutional review are met, where institutional review is required under

involves institutionalized human subjects.

(ii) When the clinical investigation is conducted on the premises of an institution that has an institutional review committee meeting the requirements of Food and Drug Administration regulations.

(iii) When the Food and Drug Administration determines that the risks to the subjects justify such review.

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§ 112.43 Selection of investigators.

(a) The sponsor shall select as investigators only individuals who, because of their training or experience, qualify as suitable experts to investigate the safety and effectiveness of the device (in view of the investigational plan, the report of prior investigations of the device, and what is known about the device) and who have the ability and commitment to comply with the investigational plan and Food and Drug Administration regulations regarding the obligations of investigators.

(b) The sponsor shall obtain from each investigator who will participate in the investigational study a signed statement for submission to the Food and Drug Administration under §§ 812.20(b) or 812.21(b)(7), which includes the following information:

(1) A statement of the investigator's education and experience in sufficient detail to allow determination of the investigator's qualifications for investigating the device. Such statement shall include:

(i) Colleges, universities, and medical or other professional schools attended, dates of attendance, degrees, and dates on which degrees were awarded.

(ii) Postgraduate medical or other professional training with dates, names of institutions, and nature of training.

(iii) Teaching or research experience, with dates, names of institutions, and a brief description of the experience.

(iv) Experience in medical practice or other professional experience, with dates, institutional affiliations, and nature of practice or other professional experience.

(v) A representative list of pertinent medical or other scientific publications of the investigator, with titles of articles, names of publications, and volume, number, page, and date.

(vi) Specific experience with the device to be investigated (when available), including date, amount, and description of experience, including the name of the institutions where investigated.

(2) An agreement to comply with the investigational plan Food and Drug Administration regulations regarding the obligations of investigators, and any conditions for approval of an application for an investigational device exemption imposed under § 812.30.

(3) An agreement that any use of the device involving human subjects will be under the investigator's supervision or under the supervision of another investigator who is responsible to him or her and who is named by the investigator in his or her signed statement under paragraph (b)(5) of this section.

(4) A statement as to whether an investigational study or other research by such investigator has been discontinued on the order of a sponsor, an institutional review committee, or the Food and Drug Administration.

(5) The name of any other investigator who will participate in the investigational study, who is under the investigator's supervision, and who is responsible to him or her, with information required in paragraph (b) (1), (2), and (4) of this section.

§ 812.45 Control over the investigational device; facilities.

The sponsor shall permit the investigational device to be shipped only to investigators who have signed statements which the sponsor has submitted to the Food and Drug Administration under §§ 812.20(a), 812.21(b)(7) or 812.39(c), and the sponsor shall comply with the requirements of Subparts C and F of Part 52 of this chapter.

§ 812.46 Monitoring the investigational study.

(a) The sponsor (other than a sponsor-investigator who is the only investigator) shall comply with the requirements of § 52.28 of this chapter in selection of and directions to trained and qualified individual(s) to monitor the progress of the investigational study. The monitor shall comply with the requirements of § 52.29 of this chapter.

(b) If the sponsor (other than a sponsor-investigator who is the only investigator) discovers that any investigator participating in the investigational study has not complied with the requirements of this part, other Food and Drug Administration regulations regarding the obligations of investigators, or such investigator's agreement under § 812.43(b), the sponsor shall secure such investigator's compliance or discontinue shipments to such investigator. The sponsor may require such investigator to make appropriate disposition of the device in accordance with § 52.114 of this chapter and may suspend or terminate any study being performed by such investigator for the sponsor.

(c) (1) The sponsor shall undertake a special investigation whenever learning of any serious adverse effect, death, or life-threatening problem that may reasonably be regarded as device-related (i.e., caused by or associated with the investigational device) and was not previously anticipated in nature, severity, or degree of incidence in the written information provided to investigators and to the Food and Drug Administration by the sponsor regarding the device. The sponsor shall report the results of the special investigation to other investigators, and to the Food and Drug Administration under § 812.55(d) within 10 working days after the sponsor learns of the effect, death, or problem.

(2) Where the sponsor learns from the special investigation that the serious adverse effect, death, or medical problem is device-related and presents unreasonable risk to subjects involved in the study, the sponsor shall suspend the study as soon as possible but in no event later than 5 working days after sufficient information is available to warrant suspension, except that if an institutional review committee or the Food and Drug Administration has ordered suspension by an earlier date, this earlier date shall apply. Suspension of an investigational study is warranted when the potential risks of continuation of the study outweigh the possible benefits. Suspension of the investigational study for purposes of this section means that no new subjects may be added to the study, and only those subjects whose medical needs require the continued use of the device may receive the device. Where the Food and Drug Administration regards a serious adverse effect, death, or medical problem as device-related and as presenting unreasonable risk to subjects, the agency may order the sponsor to suspend the study. The sponsor shall suspend the study as soon as possible but in no event later than the date prescribed in such request or order. Once the study has been suspended, the sponsor shall not resume the study without the concurrence of the Food and Drug Administration.

(d) A sponsor shall not unduly prolong an investigational study. Where data are developed in the study which would support submission of an application for premarket approval of the device pursuant to section 515 of the act, the sponsor shall either submit such an application or discontinue the study.

§ 812.47 Submitting information to investigators.

(a) The sponsor shall supply all investigators with copies of the investigational plan required under § 812.25, the report of prior investigations of the device required under § 812.27, and labeling (including labels) for the device which shall meet the requirements of § 812.5(b).

(b) The sponsor shall notify each investigator of the completion or discontinuance of the investigational study or the withdrawal of the exemption as soon as possible but in no event later than 5 working days after such action.

(c) The sponsor shall notify each investigator if an application for premarket approval of the device under section 515 of the act is approved.

(d) This section does not apply to a sponsor-investigator who is the only investigator.

§ 812.50 Promotion and sale of investigational devices.

(a) The sponsor and any person acting for or on behalf of the sponsor

will be under the investigator's supervision or under the supervision of another investigator who is responsible to him or her and who is named by the investigator in his or her signed statement under paragraph (b)(5) of this section.

(4) A statement as to whether an investigational study or other research

in the written information provided to investigators and to the Food and Drug Administration by the sponsor regarding the device. The sponsor shall report the results of the special investigation to other investigators, and to the Food and Drug Administration under § 812.55(d) within 10 working days after the sponsor learns of the effect, death, or problem.

market approval of the device under section 515 of the act is approved.

(d) This section does not apply to a sponsor-investigator who is the only investigator.

§ 812.50 Promotion and sale of investigational devices.

(a) The sponsor and any person acting for or on behalf of the sponsor

shall comply with § 52.118 of this chapter and shall not commercially distribute or test market an investigational device, until the device has been approved for marketing for the purpose for which it is being investigated.

(b) Section 52.118 of this chapter and paragraph (a) of this section shall not apply to lawful commercial shipments of a device (other than a device subject to section 520(1) of the act, i.e., a device the Food and Drug Administration had regarded as a new drug or antibiotic drug) that was in commercial distribution before May 28, 1976 or that is substantially equivalent to a device that was in commercial distribution before such date, before the device is classified under section 513(d) of the act and any transitional period for the device under section 501(f)(2)(B) of the act has expired. Section 52.118 of this chapter and paragraph (a) of this section shall, however, apply to shipments of the device for investigational use.

(c) The sponsor shall not commercialize the device by charging subjects or investigators for an investigational device if the Food and Drug Administration finds the compensation to be unreasonable in view of the manufacturing and other costs of the device itself, and has notified the sponsor of this finding.

§ 812.55 Reporting to the Food and Drug Administration, maintaining records, and permitting inspections.

(a) The sponsor shall maintain accurate and adequate records for reporting to the Food and Drug Administration on the progress of the investigational study. These reports shall be made at appropriate intervals not exceeding 1 year. Such reports shall include any significant findings of the investigational study and any amendments to the application or to previous reports that are necessary to keep them accurate and timely and that had not been submitted to the agency previously.

(b) The sponsor shall notify the Food and Drug Administration of the suspension, termination, completion or discontinuance of the investigational study within 30 working days and shall make an accurate and adequate final report to the agency on the study within 6 months after the study is suspended, terminated, completed or discontinued, or an exemption is withdrawn.

(c) The sponsor shall notify the Food and Drug Administration of any request that investigators return, or otherwise dispose of, any supplies of the investigational device and of steps taken to comply with § 52.114 of this chapter.

(d) The sponsor shall report to the Food and Drug Administration any serious adverse effect, death, or life-threatening medical problem that is subject to the requirement of a special investigation under § 812.46(c) as soon as possible, but in no event later than 10 working days after the sponsor learns of the adverse effect, death, or medical problem. The sponsor shall submit the results of the special investigation as soon as possible but in no event later than 10 working days after the special investigation is completed. Such reports shall be accurate and adequate in content.

(e) The sponsor shall submit to the Food and Drug Administration a copy of a report of a determination by an investigator under § 812.123 that informed consent cannot be obtained from a subject or the subject's legal representative. Such report shall be submitted as soon as possible but in no event later than 5 working days after such report is received from the investigator.

(f) The sponsor shall report to the Food and Drug Administration any discovery that an institutional review committee is not complying with its agreement to review the study or with applicable Food and Drug Administration regulations.

(g) The sponsor shall retain a copy of any application, report, or correspondence that the sponsor submits to the Food and Drug Administration under this part. The sponsor shall maintain copies of all communications between the sponsor and any committee or any investigator regarding the study.

(h) A sponsor may withdraw from the responsibility for maintaining records for the period of time required in § 52.195 of this chapter by transferring custody to any other person who will accept responsibility for the records, e.g., a manufacturer who has acquired the rights to the device. Notice of such transfer shall be given to the Food and Drug Administration.

(i) A sponsor shall permit an authorized employee of the Food and Drug Administration, at reasonable times and in a reasonable manner, to inspect any facilities where the investigational device is manufactured, processed, held, or used, and to inspect and copy any records of the sponsor concerning the investigational study, including any records required to be kept under this chapter to which the sponsor has the right to grant access. A sponsor shall permit a representative of an institutional review committee that is supervising all or any portion of an investigational study initiated by the sponsor, at reasonable times and in a reasonable manner, to inspect and copy any records of the sponsor relevant to the responsibilities of the committee concerning the investigational study except trade secret or confidential commercial information that is confidential as described in 21 CFR 20.61.

(j) The Food and Drug Administration may require a sponsor to submit to the agency any records concerning the investigational study, including any records required to be kept under this chapter.

Subpart D—Institutional Review Committee [Reserved]

Subpart E—Investigator Responsibilities in Investigational Studies Involving Human Subjects [Reserved]

Subpart F—Informed Consent of Human Subjects

§ 812.120 General requirements of informed consent.

(a) Except as provided in § 812.123, an investigator shall:

(1) Inform each human subject, or if the subject lacks legal capacity, the subject's legal representative, that the investigational device is being used for research purposes.

(2) Provide each human subject, or the subject's legal representative, an adequate explanation of pertinent information concerning the investigational device, including the information required in § 812.130.

(3) Obtain and document legally effective informed consent of such subject, or such subject's legal representative.

(b) Informed consent shall be obtained while the subject, or the subject's legal representative, can exercise free choice without undue inducement or the intervention of any element of force, fraud, deceit, duress, or other forms of constraint or coercion.

(c) Informed consent shall be evidenced by a written agreement and signed by the subject or the subject's legal representative.

(d) The investigator shall maintain copies of records required by this subpart for the time prescribed in § 52.195 of this chapter.

§ 812.123 Exception from requirement.

(a) The requirements of § 812.120 shall not apply when:

(1) The investigator determines in writing (i) that there exists a life-threatening situation involving the subject which necessitates the use of the investigational device, (ii) that it is not feasible to obtain informed consent from the subject, and (iii) that there is not sufficient time to obtain such consent from the subject's legal representative.

(2) Such determination has the concurrence of a licensed physician not involved in the testing of the device, unless the investigator determines, and documents these determinations, that immediate use of the device is necessary to save the life of the subject, that there is not sufficient time to obtain such concurrence, and that there is available no effective alterna-

(c) The sponsor shall notify the Food and Drug Administration of any request that investigators return, or otherwise dispose of, any supplies of the investigational device and of steps taken to comply with § 52.114 of this chapter.

(d) The sponsor shall report to the Food and Drug Administration any serious adverse effect, death, or life-threatening medical problem that is subject to the requirement of a special investigation under § 812.46(c) as soon as possible, but in no event later than 10 working days after the sponsor learns of the adverse effect, death, or medical problem. The sponsor shall submit the results of the special investigation as soon as possible but in no event later than 10 working days after the special investigation is completed. Such reports shall be accurate and adequate in content.

(2) Such determination has the concurrence of a licensed physician not involved in the testing of the device, unless the investigator determines, and documents these determinations, that immediate use of the device is necessary to save the life of the subject, that there is not sufficient time to obtain such concurrence, and that there is available no effective alterna-

tive method of therapy that is approved or generally recognized which may save the life of the subject. These determinations may be documented before use of the device or within 5 working days after use.

(b) If the investigator does not obtain informed consent and uses the investigational device in accordance with the requirements of paragraph (a) of this section, the investigator shall maintain records of, and shall report as soon as possible but in no event later than 5 working days after using the device, the determinations required by paragraph (a) (1) and (2) of this section to the sponsor, for submission by the sponsor to the Food and Drug Administration in accordance with § 812.35, and to the committee.

§ 812.130 Elements of informed consent in agreement.

(a) The investigator shall ensure that the agreement to be signed under § 812.120(c), or the information that is given to the subject or to the subject's legal representative, includes a complete explanation of pertinent information on the investigational device adequate to enable him or her to make a decision on his or her willingness to participate, or permit the subject to participate, in the investigation and also includes:

(1) A full and fair explanation of procedures to be followed, including an identification of any which are experimental.

(2) A full explanation of the nature, expected duration, and purpose of the administration of the investigational device.

(3) A description of any attendant discomforts and risks reasonably to be expected.

(4) An explanation of likely results should the procedures fail.

(5) A description of any benefits reasonably to be expected.

(6) A disclosure of any appropriate alternative procedures that might be advantageous for the subject.

(7) A description of the scope of the investigation, including the number of subjects involved in the investigational study.

(8) An offer to answer any inquiries concerning the investigational study.

(9) An instruction that the subject, or the subject's legal representative, is free to decline entrance into the investigational study or to withdraw his or her consent and to discontinue participation in the study at any time without prejudice to the subject.

(10) A statement that the investigational device is being used for research purposes.

(b) The agreement entered into by such person or his or her legal representative shall include no language through which the subject waives, or appears to waive, any of the subject's legal rights or releases or appears to release the institution or its agents, or the sponsor, or the investigator, from liability for negligence.

(c) An investigator shall provide to the sponsor and any institutional review committee participating in the review of the study a sample copy of any written materials given or read to the subject, or the subject's legal representative, regarding the information required to be given by this section and a sample copy of any form used to document the consent of such subject, or the subject's legal representative, which form shall have been approved by the committee.

Subpart G—[Reserved]

Subpart H—Tests That Do Not Involve Human Subjects

§ 812.160 Conditions of exemption.

(a) Where an investigational device is intended for use in humans, a shipment of the device that is intended solely for tests in animals used only for laboratory research purposes, or for in vitro or mechanical tests or similar tests that do not involve use of human subjects, shall be exempt from any of the otherwise applicable provisions of the act listed in § 812.1(c) if:

(1) The labeling of the device complies with the requirements of § 812.5 (a) and (b) and bears the following additional statement (or, where appropriate, a statement prescribed in § 809.10(c) of this chapter for an in vitro diagnostic product):

CAUTION—Device [or Diagnostic product] for investigational use only in laboratory animals or other tests that do not involve human subjects.

(2) The person who ships the device under this subpart uses due diligence to ensure (i) that the consignee is regularly engaged in conducting tests in animals used only for laboratory research, or for in vitro or other mechanical tests or similar tests that do not involve use of human subjects and (ii) that the shipment of the investigational device will actually be used only in such tests.

(3) The person who ships the device under this subpart maintains adequate records showing the name and address of the consignee to whom the device is shipped, date, quantity, and batch or code mark of each shipment for a period of 2 years after such shipment and, upon the request of a properly authorized employee of the Department at reasonable times, makes such records available for inspection and copying or submits such records to the Food and Drug Administration.

(4) The device will be tested in accordance with applicable requirements in Part 58 of this chapter.

(b) This subpart does not apply to any use of an investigational device that involves use of human subjects.

§ 812.170 Termination of exemption.

(a) The Commissioner shall terminate an exemption under this subpart if the Commissioner makes either of the following findings:

(1) The person shipping an investigational device under this subpart has failed to comply with one or more of the conditions for the exemption in this subpart.

(2) Any of the grounds for withdrawal of an investigational device exemption under § 812.35 applies.

(b) The Commissioner shall notify the sponsor of the termination of an exemption under this subpart by providing a full statement of the reasons for such termination and shall afford an opportunity for a regulatory hearing under Part 16 of this chapter. The person whose exemption is terminated shall recall or otherwise ensure the destruction of any unused devices.

Interested persons may, on or before September 11, 1978, submit to the Hearing Clerk (HFC-20), Food and Drug Administration, Room 4-65, 5600 Fishers Lane, Rockville, Md. 20857, written comments regarding this proposal. Four copies of all comments shall be submitted, except that individuals may submit single copies of comments, and shall be identified with the Hearing Clerk docket number found in brackets in the heading of this document.

Interested persons may file notices of appearance for a public hearing (in quadruplicate and identified with the Hearing Clerk docket number found in brackets in the heading of this document) with the Hearing Clerk on or before June 12, 1978. The date, time, and place of the hearing will be announced in the FEDERAL REGISTER. Received comments and notices of appearance may be seen in the above office between the hours of 9 a.m. and 4 p.m., Monday through Friday.

NOTE.—The Food and Drug Administration has determined that this proposal will not have a major economic impact as defined by Executive Order 11821 (amended by Executive Order 11949) and OMB Circular A-107. A copy of the economic impact assessment is on file with the Hearing Clerk, Food and Drug Administration.

Dated: April 29, 1978.

DONALD KENNEDY,
Commissioner of Food and Drugs.

[FR Doc. 78-12794 Filed 5-11-78; 8:45 am]

pation in the study at any time without prejudice to the subject.

(10) A statement that the investigational device is being used for research purposes.

(b) The agreement entered into by such person or his or her legal representative shall include no language through which the subject waives, or appears to waive, any of the subject's legal rights or releases or appears to release the institution or its agents, or the sponsor, or the investigator, from liability for negligence.

(c) An investigator shall provide to the sponsor and any institutional review committee participating in the review of the study a sample copy of any written materials given or read to the subject, or the subject's legal representative, regarding the information required to be given by this section and a sample copy of any form used to document the consent of such subject, or the subject's legal representative, which form shall have been approved by the committee.

§ 812.130 Elements of informed consent in agreement.

(a) The investigator shall ensure that the agreement to be signed under § 812.120(c), or the information that is given to the subject or to the subject's legal representative, includes a complete explanation of pertinent information on the investigational device adequate to enable him or her to make a decision on his or her willingness to participate, or permit the subject to participate, in the investigation and also includes:

(1) A full and fair explanation of procedures to be followed, including an identification of any which are experimental.

(2) A full explanation of the nature, expected duration, and purpose of the administration of the investigational device.

(3) A description of any attendant discomforts and risks reasonably to be expected.

(4) An explanation of likely results should the procedures fail.

(5) A description of any benefits reasonably to be expected.

(6) A disclosure of any appropriate alternative procedures that might be advantageous for the subject.

(7) A description of the scope of the investigation, including the number of subjects involved in the investigational study.

(8) An offer to answer any inquiries concerning the investigational study.

(9) An instruction that the subject, or the subject's legal representative, is free to decline entrance into the investigational study or to withdraw his or her consent and to discontinue participation in the study at any time without prejudice to the subject.

(10) A statement that the investigational device is being used for research purposes.

(b) The agreement entered into by such person or his or her legal representative shall include no language through which the subject waives, or appears to waive, any of the subject's legal rights or releases or appears to release the institution or its agents, or the sponsor, or the investigator, from liability for negligence.

(c) An investigator shall provide to the sponsor and any institutional review committee participating in the review of the study a sample copy of any written materials given or read to the subject, or the subject's legal representative, regarding the information required to be given by this section and a sample copy of any form used to document the consent of such subject, or the subject's legal representative, which form shall have been approved by the committee.

Subpart G—[Reserved]

Subpart H—Tests That Do Not Involve Human Subjects

§ 812.160 Conditions of exemption.

(a) Where an investigational device is intended for use in humans, a shipment of the device that is intended solely for tests in animals used only for laboratory research purposes, or for in vitro or mechanical tests or similar tests that do not involve use of human subjects, shall be exempt from any of the otherwise applicable provisions of the act listed in § 812.1(c) if:

(1) The labeling of the device complies with the requirements of § 812.5 (a) and (b) and bears the following additional statement (or, where appropriate, a statement prescribed in § 809.10(c) of this chapter for an in vitro diagnostic product):

CAUTION—Device [or Diagnostic product] for investigational use only in laboratory animals or other tests that do not involve human subjects.

(2) The person who ships the device under this subpart uses due diligence to ensure (i) that the consignee is regularly engaged in conducting tests in animals used only for laboratory research, or for in vitro or other mechanical tests or similar tests that do not involve use of human subjects and (ii) that the shipment of the investigational device will actually be used only in such tests.

(3) The person who ships the device under this subpart maintains adequate records showing the name and address of the consignee to whom the device is shipped, date, quantity, and batch or code mark of each shipment for a period of 2 years after such shipment and, upon the request of a properly authorized employee of the Department at reasonable times, makes such records available for inspection and copying or submits such records to the Food and Drug Administration.

(4) The device will be tested in accordance with applicable requirements in Part 58 of this chapter.

(b) This subpart does not apply to any use of an investigational device that involves use of human subjects.

§ 812.170 Termination of exemption.

(a) The Commissioner shall terminate an exemption under this subpart if the Commissioner makes either of the following findings:

(1) The person shipping an investigational device under this subpart has failed to comply with one or more of the conditions for the exemption in this subpart.

(2) Any of the grounds for withdrawal of an investigational device exemption under § 812.35 applies.

(b) The Commissioner shall notify the sponsor of the termination of an exemption under this subpart by providing a full statement of the reasons for such termination and shall afford an opportunity for a regulatory hearing under Part 16 of this chapter. The person whose exemption is terminated shall recall or otherwise ensure the destruction of any unused devices.

Interested persons may, on or before September 11, 1978, submit to the Hearing Clerk (HFC-20), Food and Drug Administration, Room 4-65, 5600 Fishers Lane, Rockville, Md. 20857, written comments regarding this proposal. Four copies of all comments shall be submitted, except that individuals may submit single copies of comments, and shall be identified with the Hearing Clerk docket number found in brackets in the heading of this document.

Interested persons may file notices of appearance for a public hearing (in quadruplicate and identified with the Hearing Clerk docket number found in brackets in the heading of this document) with the Hearing Clerk on or before June 12, 1978. The date, time, and place of the hearing will be announced in the FEDERAL REGISTER. Received comments and notices of appearance may be seen in the above office between the hours of 9 a.m. and 4 p.m., Monday through Friday.

NOTE.—The Food and Drug Administration has determined that this proposal will not have a major economic impact as defined by Executive Order 11821 (amended by Executive Order 11949) and OMB Circular A-107. A copy of the economic impact assessment is on file with the Hearing Clerk, Food and Drug Administration.

Dated: April 29, 1978.

DONALD KENNEDY,
Commissioner of Food and Drugs.

[FR Doc. 78-12794 Filed 5-11-78; 8:45 am]

University of Pittsburgh

SCHOOL OF MEDICINE
Department of Neurological Surgery

February 19, 1979

BROWDY & NEIMARK
RECEIVED
FEB 21 1979
WASHINGTON, D. C.

Mr. Norman Latker
1233 Munsuy Building
1329 E Street
Washington, D.C. 20004

Dear Mr. Latker:

This will confirm our various telephone conversations with regard to the upcoming AAMI meeting. I wish to thank you for myself and on the behalf of the AAMI for your willingness to participate in the AAMI meeting. As I indicated the session will be held on the day following my Implantable and Indwelling Biosensors session where short research reports will be presented. Your presentation will be in a session beginning at 5:30 on Tuesday, May 22, 1979, and will be one of three to be followed by a short period for the various speakers to react with each other and for audience participation. I am enclosing copies of the program, both of the Monday Implantable and Indwelling Biosensor research session and of the Tuesday afternoon session in which you will participate. Dr. Bessman will talk about special problems in design and engineering of a particular type of implantable medical device (the artificial metabolic pancreas). Mr. Link will discuss the view of the FDA, hopefully with a special thrust to the role that the investigator himself can play in easing the project through the regulatory phase in order to reduce the overall time and expense of accomplishing this and I want you to feel free to express the views that you have on this subject including the impact of regulation upon research and upon the investigator, the role of patent ability, the advisibility of patenting these developments, and the way in which academia and industry can hopefully work together to overcome potential obstacles relating to both patent protection and to federal regulation. I make these suggestions merely to try and tie the three presentations together, but I do not mean to limit you in any way and want you to speak on what aspects of this general subject with which you feel most comfortable and most expert. I realize that the three participants may not necessarily agree and look forward to them reacting to each other's presentation in the discussion session which will round out the presentations. There will also be time for audience questioning and discussion.

The organization of the AAMI meeting provides for the publication of a proceedings composed of one page abstracts or short papers. I am enclosing a xerox copy of the official abstract form and would like to encourage you to provide an abstract. Please fill up all the space provided as much as possible so as to allow a balanced printed end product.

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MONTEFIORE HOSPITAL, 3459 FIFTH AVE., PITTSBURGH, PA. 15213 • (412) 683-1100 EXT. 487



The method of reproduction is such that any blanks left within the boxes will appear as blank space in the final copy. Thus, it would be best to adjust the length of the abstract so as to use most, if not all, the space provided in both columns (an empty column will appear as such in the final printed copy). I will have all the abstracts retyped in my office for uniformity and must send these out by March 1. Thus, it would be best to forward the abstract to me as soon as possible.

As I indicated, I will be able to provide you with a $400.00 honorarium to help defray the expenses of coming to Las Vegas. This will be provided at the time of the meeting or shortly thereafter. I am enclosing copies of both the session in which you will participate and the research session of the day before and would certainly invite you to attend that session as well if possible. Also enclosed is a preliminary announcement about the overall meeting, which includes on page 14 and 15 forms for hotel reservation and for registration. As an invited speaker, your registration fee will be waved and you will be pre-registered. Thus, you need only fill this one out if you wish to be involved in the social program, short courses, etc. You should hear from AAMI regarding your needs for audiovisual aids.

If you have any questions, please do not hesitate to contact me directly. Thanks again for your participation.

Sincerely,

Dictated by Sidney K. Wolfson, Jr., M.D.
Professor of Neurosurgery and Surgery
Director of Surgical Research
Signed in his absence

SKW:llj

Enclosures