

franchises is not necessary to prevent the unfair or deceptive acts or practices to which the Rule relates.

Accordingly, the Commission has determined that the provisions of 16 CFR Part 436 shall not apply to the advertising, offering, licensing, contracting, sale or other promotion of truck dealerships by Navistar International Transportation Corporation.

It is so ordered.

By the Commission.

Issued: November 10, 1998.

List of Subjects in 16 CFR Part 436

Trade practices and franchising.

Donald S. Clark,

Secretary.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 812

[Docket No. 98N-0394]

RIN 0910-ZA14

Medical Devices; Investigational Device Exemptions

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is amending the Investigational Device Exemptions (IDE) regulation. The regulatory changes are intended to reflect amendments to the Federal Food, Drug, and Cosmetic Act (the act) by the FDA Modernization Act of 1997 (FDAMA). These amendments provide that the sponsor of an IDE may modify the device and/or clinical protocol, without approval of a new application or supplemental application, if the modifications meet certain criteria and if notice is provided to FDA within 5 days of making the change. The rule also defines the credible information to be used by sponsors to determine if the criteria are met.

EFFECTIVE DATE: February 22, 1999.

FOR FURTHER INFORMATION CONTACT: Joanne R. Less, Center for Devices and Radiological Health (HFZ-403), Food and Drug Administration, 9200 Corporate Blvd., Rockville, MD 20850, 301-594-1190.

SUPPLEMENTARY INFORMATION:

I. Background

Experience has shown that during the course of a clinical investigation, the sponsor of the study will often want or need to make modifications to the investigational plan, including changes to the device and/or the clinical protocol. These changes may be simple modifications, such as clarifying the instructions for use, or they may be significant changes, such as modifications to the study design or device design.

The IDE supplement regulation that has been effect since 1985 (hereinafter referred to as the "existing regulation"), § 812.35(a) (21 CFR 812.35(a)), states in part:

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

Under § 812.25 *Investigational plan* (21 CFR 812.25), the investigational plan includes: (1) The purpose of the study, (2) the clinical protocol, (3) a risk analysis, (4) a description of the investigational device, (5) monitoring procedures, (6) labeling, (7) informed consent materials, and (8) institutional review board (IRB) information. Although written guidance on the types of modifications that can be made without prior FDA approval has not previously been developed, the agency has permitted changes to all parts of the investigational plan, without new or supplemental IDE application approvals, if the changes did not affect the scientific soundness of the plan or the rights, safety, or welfare of the subjects, and if such changes were reported to FDA in the upcoming annual report under § 812.150(b)(5) (21 CFR 812.150(b)(5)).

On November 21, 1997, the President signed into law FDAMA. Section 201 of FDAMA (Pub. L. 105-115) amended the act by adding new section 520(g)(6) to the act (21 U.S.C. 360j(6)). Section 520(g)(6) of the act permits, upon issuance of a regulation, certain changes to be made to either the investigational device or the clinical protocol without prior FDA approval of an IDE supplement. Specifically, this section of the statute permits:

(i) developmental changes in the device (including manufacturing changes) that do not constitute a significant change in design or in the basic principles of operation and that are made in response to information

gathered during the course of an investigation; and

(ii) changes or modifications to clinical protocols that do not affect—

(I) the validity of the data or information resulting from the completion of an approved protocol, or the relationship of likely patient risk to benefit relied upon to approve a protocol;

(II) the scientific soundness of an investigational plan submitted [to obtain an IDE]; or

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

The existing IDE regulation and the new statute both permit certain changes to be made to the investigational plan without prior agency approval. FDA views the changes and modifications allowed under section 520(g)(6) of the act as consistent with the way the agency has previously interpreted existing § 812.35(a).

Section 520(g)(6) of the act, as added by FDAMA, also specifies that the implementing rule provide that such changes or modifications may be made without prior FDA approval if the IDE sponsor determines, on the basis of credible information (as defined by the Secretary of Health and Human Services (the Secretary)) that the previous conditions are met and if the sponsor submits, not later than 5 days after making the change or modification, a notice of the change or modification. Lastly, section 520(g)(6) of the act requires that FDA issue a final regulation implementing this section no later than 1 year after the date of enactment of FDAMA.

On July 15, 1998 (63 FR 38131), FDA issued a proposal to implement section 520(g)(6) of the act. FDA provided interested persons an opportunity to comment on the proposed rule by September 28, 1998. FDA received comments from five entities; one medical device manufacturer's association, two medical device manufacturers, one law firm, and one consumer. Most of the comments stated that the proposed regulation increased the economic and regulatory burden and lacked flexibility compared to the existing regulation. FDA has revised the proposed regulation in several significant respects to address these concerns. The following is a summary of the comments and FDA's response to them.

II. Summary and Analysis of Comments and FDA's Responses

A. General Comments

1. Several comments objected to FDA's proposal because it would require that notices be submitted within 5 days of implementing protocol and device changes that had previously been

submitted in annual reports under the existing § 812.35(a)(1). Comments stated that the regulation should instead have required 5-day notices for changes that were formerly submitted as IDE supplements. These comments asserted that the proposed rule was not consistent with the intent of the statute which was to reduce the burden on industry by decreasing the number of submissions requiring prior agency approval. Another comment contended that submitting a notice within 5 days of implementation of a change rather than in an annual report would pose a regulatory and economic burden for industry.

FDA recognizes that some of the protocol and device changes that were previously submitted in IDE annual reports will now need to be submitted in a 5-day notice under the new regulation. For the reasons described in the following paragraphs, however, FDA believes that the language in new section 520(g)(6) of the act clearly requires this, but does not believe that the new regulation will impose any appreciable additional burden.

Prior to the enactment of section 520(g)(6) of the act, the criteria that had been used to determine whether a change to an investigational plan required approval of an IDE supplement were described in existing § 812.35(a)(1). This section of the IDE regulation required a supplement if the change to the investigational plan "may affect its scientific soundness or the rights, safety, or welfare of such subjects." All changes that were deemed not to affect scientific soundness or the rights, safety, or welfare of the subjects could be implemented without FDA approval of an IDE supplement, and instead were reported to the agency in an annual report under § 812.150(b)(5).

As stated in the preamble to the proposed rule, the agency has permitted changes to all parts of the investigational plan, including the device, manufacturing process, and clinical protocol, without new or supplemental IDE application approvals if the changes were made in compliance with existing § 812.35(a)(1) and if the changes were reported to FDA in the upcoming annual report. Because written guidance specifying the types of modifications that could be made without prior approval has never been issued, there was some inconsistency in the determination of which types of changes could be permitted without the submission of a supplement. Therefore, some changes which may have met the criteria for submission in an annual report were submitted for prior approval in an IDE supplement.

Section 520(g)(6) of the act, in describing the types of protocol changes that were to be subject to 5-day notices, incorporated verbatim the "scientific soundness" and "rights, safety, or welfare" criteria in existing § 812.35(a)(1) that distinguished those changes that required prior approval from those that could have been submitted in an annual report. This section of the act also sets forth additional criteria for changes that would qualify for implementation with a 5-day notice. These additional criteria are consistent with the criteria in the existing regulation that have been used to determine the effect of a change on the scientific soundness of the investigational plan and the rights, safety, and welfare of subjects. Thus, the language in section 520(g)(6) of the act requires that some changes that had previously been submitted in annual reports will now need to be submitted within 5 days of implementation.

FDA disagrees that the new regulation will be more burdensome for industry. Section 520(g)(6) of the act and the new implementing regulation reduce the burden on industry in two important ways. First, section 520(g)(6) of the act makes mandatory FDA's previous practice of permitting certain changes to be made to the investigational plan without prior agency approval. Secondly, this regulation provides clarification of the types of changes that could be implemented without prior agency approval, thus eliminating the submission of IDE supplements that are not needed. For example, prior to this implementing regulation, an IDE supplement may have been submitted for any materials change to an investigational device. The new regulation, however, clarifies that approval of a supplement would only be needed if the materials change represents a significant change in design (e.g., new risks) or basic principles of operation.

Finally, FDA disagrees that notifying the agency of a change within 5 days of implementation, rather than in an annual report, will pose a regulatory and economic burden on industry. FDA is aware that submitting a notice within 5 days, as required by section 520(g)(6)(B)(ii) of the act, represents a much shorter response time compared to submission in an annual report. FDA does not believe, however, that this reduced timeframe will impose any appreciable additional burden to industry as the evidence used to determine whether a change may be made under an annual report or the 5-day notice provision is the same, and in both cases, would need to be generated

and evaluated before the change is implemented.

2. One comment stated that section 520(g)(6) of the act should be interpreted to allow a sponsor to make device changes that significantly improve safety or effectiveness, yet do not constitute significant changes in design or in the basic principles of operation under the 5-day notice provision.

FDA agrees that section 520(g)(6) of the act allows a sponsor to make device changes intended to enhance significantly safety or effectiveness without submitting an IDE supplement, if the developmental changes in a device do not constitute significant changes in design or in the basic principles of operation. Although the comment was not entirely clear, it also seems to suggest that any change intended to enhance safety or effectiveness should not require an IDE supplement. If this were the suggestion, FDA does not agree. Consistent with all other device statutory and regulatory product approval provisions, section 520(g)(6) of the act does not condition the submission of an IDE supplement on whether a change will enhance safety or effectiveness. Section 520(g)(6) of the act conditions the use of the 5-day notice provision only on whether the change is a significant change in the design or basic principles of operation. An interpretation that 5-day notices are allowed any time a sponsor intends a change to enhance safety or effectiveness would not only be contrary to the language in section 520(g)(6) of the act, it would constitute a drastic change in FDA's longstanding position that the statute and regulations require either a new premarket notification, new premarket approval application, or new IDE for certain types of device modifications regardless of whether the sponsor believes the changes enhance safety or effectiveness. Manufacturers make most modifications with the intention and belief that the change will make a safer and/or more effective product. This factor does not obviate the need for FDA to review changes to ensure that there is scientific support to show that safety and effectiveness have not been compromised.

3. One comment asked that an open public meeting be convened to discuss the proposed rule with knowledgeable representatives of all affected entities.

FDA disagrees that such a meeting is necessary. Detailed comments were received on virtually every aspect of the proposed regulation, and the agency has significantly revised the rule in accordance with the concerns that were expressed in the comments. As

discussed in detail in the following paragraphs, the final rule provides for more flexibility than the proposed rule and addresses the concerns regarding the economic and regulatory burden posed by the proposed regulation.

B. Proposed § 812.35(a)(1) Changes Requiring Prior Approval

4. One comment stated that the first sentence of this proposed section is awkward and suggested that it be revised to read:

Except as described in paragraphs (a)(2) through (a)(4) of this section, a sponsor must receive approval of a supplemental application under § 812.30(a), and IRB approval when appropriate under 21 CFR Part 56, prior to implementing a change to an investigational plan for a device which is subject to an approved IDE.

FDA agrees that the proposed sentence could be simplified and more clearly stated. Therefore, the agency has revised the sentence to read:

Except as described in paragraphs (a)(2) through (a)(4) of this section, a sponsor must obtain approval of a supplemental application under § 812.30(a), and IRB approval when appropriate (see §§ 56.110 and 56.111 of this chapter), prior to implementing a change to an investigational plan.

5. One comment objected that proposed § 812.35(a)(1) would require IDE supplements for changes where only annual reports had been required under the existing regulation. Specifically, the comment objected to the language in proposed § 812.35(a)(1) which states that a supplement is required when "the sponsor or an investigator proposes a change in the investigational plan." The comment stated that the language in the existing regulation only required supplements for changes in an investigational plan that "may affect its scientific soundness or the rights, safety, or welfare of subjects."

FDA does not intend new § 812.35(a)(1) to require the submission of an IDE supplement for changes that would have been submitted in an annual report under the existing regulation. Proposed and final § 812.35(a)(1) states "Except as described in paragraphs (a)(2) through (a)(4) of this section, * * *." Section 812.35(a)(3) and (a)(4) provide that sponsors do not have to submit an IDE supplement for changes to an investigational plan that do not affect the scientific soundness, rights, safety, or welfare of subjects, risk to benefit relationship relied upon to approve the protocol, or validity of the data. As stated in the preamble to the proposed rule, FDA considers the two additional criteria, i.e., risk to benefit relationship

and validity of the data, to be consistent with the agency's general criteria under the existing regulation that permits changes to the investigational plan as long as the changes do not compromise patient rights, safety, or welfare or the integrity of the clinical trial.

C. Proposed § 812.35(a)(3)(i) Developmental Changes

6. In the proposed rule, the first sentence of § 812.35(a)(3)(i) stated "The requirements in paragraph (a)(1) of this section regarding FDA and IRB approval of a supplement do not apply to developmental changes in the device (including manufacturing changes) * * *." FDA has modified this sentence to remove the phrase "and IRB." Therefore, the sentence now reads "The requirements in paragraph (a)(1) of this section regarding FDA approval of a supplement do not apply to developmental changes in the device (including manufacturing changes) * * *."

The agency has modified the regulation in this manner as the proposed language indicated that IRB approval and/or notification to the IRB of device/manufacturing changes in an annual report was not required. This language not only conflicted with the language in proposed § 812.35(a)(3)(iv), but also conflicted with 21 CFR 56.108(a)(4) which indicates that IRB's may require review of changes to approved research. FDA would like to clarify that while developmental changes that are made in accordance with section 520(g)(6) of the act do not need FDA approval, they must still be reported to the IRB in the sponsor's annual report. Moreover, the changes may be subject to IRB review under § 56.110 (21 CFR 56.110).

D. Proposed § 812.35(a)(3)(iii)(A) Definition of Credible Information (Device/Manufacturing Changes)

7. In this section of the proposed regulation, FDA defined "credible information," upon which sponsors are to rely in assessing device/manufacturing changes, as the information generated under the design control provisions § 820.30 (21 CFR 820.30) of the Quality System (QS) Regulation. (The QS regulation implements FDA's good manufacturing practice (GMP) authority of section 520(f) of the act.) One comment contended that the agency does not have the authority to require IDE sponsors to comply with design controls. Specifically, the comment said that while § 812.1(a) (21 CFR 812.1(a)) states that "investigational devices are exempt from section 520(f) of the Act, except for

the requirements under 21 CFR 820.30, most device counsels advise their clients that this regulation does not take precedence over the explicit exemption from section 520(f) found in section 520(g)(2)(A) of the statute."

FDA does not agree. It interprets the act as authorizing it to require IDE sponsors to comply with the design control procedures, as stated in § 812.1(a). Contrary to the comment's assertion, section 520(g)(2)(A) of the act does not categorically exempt investigational devices from all GMP requirements. Section 520(g)(2)(A) of the act states that FDA shall issue regulations that "prescribe procedures and conditions under which devices intended for human use *may* upon application be granted an exemption from the requirements of * * * subsection (f) of this section * * *." (Emphasis added). Section 520(g)(2)(A) of the act does not mandate that FDA issue regulations that exempt investigational devices from the act's other requirements, but rather it allows FDA discretion in issuing IDE's from other statutory requirements. Under this discretionary authority, FDA has chosen to retain design control requirements for investigational devices as stated in § 812.1(a). The agency believes that it would be illogical to exclude investigational devices used in clinical trials from the design control provision of the QS regulation because clinical trials are an integral part of the device development process.

8. Other comments generally supported the use of design controls but stated that, while design controls may be one acceptable method of supporting developmental changes in a device, sponsors should not be limited to or required to use design controls to support this type of change. Two comments suggested that FDA should follow more closely the definition of "credible information" in the legislative history, namely: "'credible information' shall mean information upon which a reasonable person in a manufacturer's position would rely upon in making a decision to change or modify an investigational device" (Food and Drug Administration Modernization and Accountability Act of 1997, S. Rept. No. 105-43, at 32 (July 1, 1997)). One comment suggested that the definition be revised to include "any other reasonable and reliable means," while a second comment recommended "literature, design controls, validation studies, or other appropriate means."

FDA agrees that limiting the definition of credible information for developmental changes for a device to the information generated under design

controls procedures is overly restrictive and recognizes that other information may serve as the credible information. Therefore, rather than limit the definition of credible information for device/manufacturing changes to design controls, the agency has revised the definition to also include information such as preclinical/animal testing, peer reviewed published literature, or other reliable information such as clinical information gathered during the trial or from marketing experience gained in other countries. FDA believes this new definition is consistent with the legislative history discussing the term "credible information," but provides more specific guidance to IDE sponsors.

9. Several other comments questioned specific aspects of the design control process, such as the need for the completion of all verification and validation testing prior to implementation of the change, the apparent requirement that a device's original design input requirements cannot be modified, and FDA's definition of "new types of risks."

FDA agrees, in part, with the comments. With regard to the assertion that FDA is requiring that all verification and validation testing be completed before a device/manufacturing change is implemented, the agency recognizes that verification and validation testing depends upon the type of change that is made, and that for some minor changes, no such testing may be needed. In addition, the agency acknowledges that the clinical trial itself may be part of the validation testing. Thus, it would be impractical to require that this testing, or other verification or validation testing that would reasonably occur after the clinical trial, be completed before a device/manufacturing change is implemented. In response to the comments, the regulation has been modified to state "verification and validation testing, as appropriate."

FDA believes that the comment that asserted that the proposed regulation requires that a device's original design input requirements remain unchanged, reflects a misunderstanding of the proposed regulation. FDA recognizes that if a sponsor is modifying the device design and/or the manufacturing process, the design input requirements would need to be modified until the design is finalized. Thus, the sponsor should conduct the appropriate verification and validation testing and this testing should indicate that the design outputs meet the modified design input requirements. The agency believes that this explanation will serve

to clarify the issue and no change to the regulation is necessary.

With respect to the agency's interpretation of the term "new types of risks," FDA is providing the following clarification. In the preamble to the proposed rule, FDA stated that if a sponsor determined that no new types of risks were introduced by the device/manufacturing change and the subsequent verification and validation testing demonstrated that the design outputs met the design input requirements, then the change could be made without prior agency approval. An example of two materials changes in a catheter was provided to illustrate this. One change, from polyvinylchloride (PVC) to silicone, would be permitted under a 5-day notice because no new types of risks resulted from the change; and one, from PVC to latex, would require prior approval because a new type of risk, i.e., possible latex sensitivity, would result from the change. A comment stated that the example was unclear because changing from PVC to silicone and from PVC to latex presented the same two types of risks (biocompatibility and materials sensitivity). The comment requested that a definition of "new types of risks" be provided since, in the example, the agency failed to recognize materials sensitivity in the PVC to silicone change as a new type of risk.

FDA acknowledges that this example was not clear and that for both materials changes, materials sensitivity should have been identified as a new type of risk. The agency agrees with the comment's assessment of "new types of risks" in the previous example. Because the evaluation of whether new types of risks are presented will vary depending on the type of device and the type of change, FDA does not believe that this term should be defined in the regulation.

10. One comment objected to a statement in the preamble that indicated that manufacturers should also conduct other testing that addresses concerns that may have been identified to the IDE sponsor in a "recognized standard." The comment stated standards are strictly voluntary and FDA should not require manufacturers to conform with them.

FDA agrees that standards are voluntary and thus, FDA cannot require IDE sponsors to conform to them. FDA did not state, however, that the sponsor is required to conform to a voluntary standard, instead FDA stated only that a sponsor "should conduct any other performance testing that addresses a safety or performance concern that may have been identified to the IDE sponsor in a recognized standard or other agency

correspondence." (Emphasis added). Although FDA recognizes that compliance with a voluntary standard is not required to address safety or performance concerns, compliance with standards may be one way, among others, of addressing those concerns. It should be noted, however, that if a manufacturer chooses a recognized standard as a device input requirement, the device output should meet that standard.

11. Comments were received both in support of and in opposition to the agency's reference to the guidance document entitled "Deciding When to Submit a 510(k) for a Change to an Existing Device." Two comments agreed that this guidance would be helpful to sponsors when deciding what types of changes could be made under the 5-day notice provision. One comment questioned the relevance of the guidance to the proposed rule as changes that can be made to marketed devices without affecting their safety and effectiveness may not be appropriate types of changes for investigational devices. Lastly, one comment appears to have misunderstood the agency's intent in referring to the guidance. It was asserted that the document would be helpful in determining the significance of a change, but would be overly restrictive in the types of changes that would be permitted under the 5-day notice provision.

In response to the comments which opposed the agency's reference to the guidance document, FDA is offering the following clarification. As stated in section 520(g)(6)(A)(i) of the act, only those changes to the investigational device that do not constitute a significant change in design or basic principles of operation are eligible for implementation under this provision. In an effort to describe the types of device and manufacturing changes that may be eligible for implementation without FDA approval, reference was made to the 510(k) guidance document. This guidance was referenced only for its list of generic types of device and manufacturing changes that the agency believes apply to all devices, marketed or investigational. The list includes the control mechanism, principle of operation, energy type, environmental specifications, performance specifications, ergonomics of patient-user interface, dimensional specifications, software or firmware, packaging or expiration dating, sterilization, and the manufacturing process (including the manufacturing site). In referencing these types of changes, the agency was not indicating

that any specific change within a particular type would or would not be appropriate under the 5-day notice provision because changes in each of these categories could range from minor to significant depending upon the particular device, the type of modification, and the extent of the modification. FDA maintains that IDE sponsors should refer to the list as a starting point for the types of changes which may qualify for implementation under this provision. The impact of the change, however, would still need to be determined by information generated by design controls or other appropriate means to assess the significance of the change to the device design or manufacturing process and the appropriateness of a 5-day notice submission.

FDA notes, however, that it believes one type of change should be submitted in an IDE supplement. In the preamble to the proposed rule, the agency stated that it would consider any change to the basic principles of operation of a device to be highly likely to constitute a significant change requiring prior approval and solicited comments on this premise. FDA received no comments on this issue. The agency advises that it considers all changes to the basic principles of operation of a device to be significant changes that should be submitted in an IDE supplement.

E. Proposed § 812.35(a)(3)(iii)(B) Definition of Credible Information (Protocol Changes)

12. Several comments questioned the agency's definition of credible information for protocol changes as defined in proposed § 812.35(a)(3)(iii)(B). In general, the comments stated that the requirement to obtain the approval of an IRB chairperson (or designee) or of a data safety monitoring board (DSMB) will result in considerable expense, is unduly burdensome and time consuming, and is less flexible than the current regulation. The comments asserted that FDA did not adequately consider the cost of imposing such a requirement. In addition, the comments contended that section 520(g)(6)(B)(i) of the act identifies the sponsor as the party responsible for determining whether a protocol change needs FDA approval, not a third party. In addition to the general concerns, specific concerns were raised regarding the use of DSMB's. It was asserted that since DSMB's are neither required nor recognized in the IDE regulation and FDA has no regulatory authority over them, DSMB's should not be included

in the agency's definition of credible information for protocol changes.

Upon further consideration of this statutory provision, the agency agrees that requiring approval of the IRB chairperson (or designee) and/or concurrence of a DSMB in the definition of credible information for protocol changes could prove more burdensome than Congress intended. FDA also agrees that the act indicates that the sponsor is responsible for initially determining if the change meets the statutory criteria. Therefore, FDA has modified the regulation to state that credible information to support changes to the clinical protocol is defined as the sponsor's documentation supporting its conclusion that the change does not have a significant impact on the study design or planned statistical analysis, and that the change does not affect the rights, safety, or welfare of the subjects. Such a determination should be made by the person in the company responsible for such decisions and should be based upon information such as peer reviewed published literature, the recommendation of the clinical investigator(s), and or data collected during the clinical trial or marketing in other countries.

As an example of this, consider a case in which preliminary information gathered during the clinical trial indicates that the inclusion/exclusion criteria should be modified to better define the target patient population. This change could be made after the sponsor concludes and documents that the change would not have a significant impact on the study design or planned statistical analysis and that the change does not affect the rights, safety, or welfare of the study subjects. Similarly, if the clinical investigators recommended that the protocol be modified to lengthen the subject followup, this change could be implemented after the previous assessments are performed that support a determination that the change is not significant.

As discussed in the preamble to the proposed rule, other examples of protocol modifications that could be made under the 5-day notice provision include: Increasing the frequency at which data or information is gathered, modifying the protocol to include additional patient observations/measurements, and modifying the secondary endpoints. Alternatively, FDA believes that the following types of protocol changes would not generally be appropriate for implementation without prior agency approval because they are likely to have a significant effect on the scientific soundness of the trial design

and/or validity of the data resulting from the trial: Change in indication, change in type or nature of study control, change in primary endpoint, change in method of statistical evaluation, and early termination of the study (except for reasons related to patient safety).

FDA notes that, contrary to statements in the proposed rule (63 FR 38131 and 38134), protocol changes involving study expansions should not be made without prior agency approval. In the proposed rule, FDA stated that sponsors could increase either the number of investigational sites or study subjects participating in a clinical investigation without approval of an IDE supplement. Upon reconsideration, the agency believes that expanding the study in either manner affects the rights, safety, and welfare of the subjects. Thus, FDA believes that this type of protocol change does not meet the statutory criteria and may not be implemented without submission and approval of an IDE supplement.

Finally, it should be noted that while FDA is not requiring IRB approval or DSMB concurrence to be used as the credible information to support protocol changes, sponsors may use this information if they so wish. In addition, depending upon the type of protocol change being considered, approval by the IRB may be required under § 56.110.

F. Proposed § 812.35(a)(3)(iv) Notice of IDE Change

13. Several comments suggested that FDA should make it clear that the 5-day timeframe consists of 5-working days and not 5-calendar days, because 5-calendar days is unreasonably short and could consist of as few as 2-working days. Another comment suggested that the rule should state that the notice need only be mailed within 5 days and not necessarily received by FDA within that time.

The agency agrees with the comments regarding working rather than calendar days and has modified the regulation to indicate that the notices shall be submitted within 5-working days. FDA also agrees that sponsors have 5 days from the time a change is implemented to mail the notice. The agency disagrees, however, that the regulation should be modified because unless otherwise specified, agency timeframes already generally indicate the time to mailing rather than the time to receipt.

14. One comment suggested that the requirements for the contents of a notice of IDE change were unduly burdensome in that the statute required a notice and not a detailed description of the changes. The comment further

suggested that FDA should require only a notice of the change, while the detailed description would be reported in the annual report.

FDA disagrees with the comment. As modified in the final rule, the information to be submitted to the agency in the notice is the same information that the sponsor would have submitted in the annual report and therefore, should not represent an increased burden. The recommendation that sponsors should be permitted to submit a simple notice of the change in 5 days, followed by a full description in the annual report, would not allow the agency to review the notices in a timely fashion, as other comments asserted was critical to this provision (see section II.G of this document).

G. Proposed § 812.35(a)(3)(v) Review of the Notices

15. Several comments objected that the proposed rule did not contain any procedures or timeframes within which FDA would review and respond to the notices. The comments stated that this omission was unfair to manufacturers and would result in uncertainty that could lead to the submission of more supplements by manufacturers who wanted certainty that the data could be used in support of a premarket application. It was also asserted that the proposed approach does not serve the public health and recommended that the provision be revised to include an appropriate timeframe within which the agency would respond to the IDE sponsor if additional information to support the change is needed. Comments suggested various time periods in which FDA should respond to the notices, ranging from 5 days to 30 days.

FDA agrees, in part, with the comments. Upon reconsideration, the agency agrees that procedures should be identified for the review of the IDE notices. FDA intends to review the notices in the same timeframe and manner in which it has customarily reviewed other IDE submissions of this type, i.e., progress/annual reports. In keeping with its practice for other submissions of this type, the agency will only notify the sponsor if questions arise or additional information is needed.

FDA disagrees that a specific timeframe for review, such as a 5 or 10-day period, should be established in the final rule. The statute does not require that FDA conduct its review of the notices within a specific period of time. As stated previously, the agency will make every effort to review the notices in the same timeframe and manner as it

does other IDE submissions. FDA believes that with the majority of the notices, it will be readily apparent whether the notice meets the applicable criteria. In those instances in which questions arise, the agency will address the issue as expeditiously as possible, thereby ensuring the protection of public health.

It should be noted that FDA reserves the right to request additional information if, during the course of the investigation, information becomes available (e.g., adverse events) that would cause the agency to question whether the change(s) made in accordance with § 812.35(a)(3)(i) or (a)(3)(ii) met the applicable criteria. FDA would normally only take such action if the agency believes that the modification to the device, manufacturing process, or protocol could jeopardize patient safety, the scientific soundness of the investigation, or the validity of the data resulting from the trial.

H. Proposed § 812.35(a)(4) Changes Submitted in an Annual Report

16. One comment stated that proposed § 812.35(a)(4) was difficult to understand and suggested that it be rewritten to express in the regulation the preamble's discussion of annual report requirements.

FDA agrees, in part, with the comment. The agency agrees that this section of the regulation could be simplified and has revised § 812.35(a)(4) in the final rule to more clearly indicate the types of changes to the investigational plan that are suitable for submission in an annual report. The agency disagrees, however, that the regulation should include all of the text from the preamble of the proposed rule. The discussion from the preamble of the types of changes that would be appropriate for submission in an annual report is too detailed to be included in a regulation. Furthermore, this list was intended to be illustrative rather than all inclusive; including it in the regulation would be overly restrictive.

17. One comment noted that the proposed rule failed to include a provision that would assure manufacturers that their data could be used in support of a premarket application as suggested in the legislative history. Specifically, the comment noted that the proposed rule did not reference section 515(d)(B)(iii) of the act (21 U.S.C. 360e(d)(B)(iii)), and stated that the agency should modify the regulation to state: "FDA will accept and review all data and information that are derived in accordance with this section in determining whether to clear

or approve a device for commercial distribution." The comment maintains that this addition to the regulation would clarify that FDA will accept and review the data if the IDE sponsor determines that no new original or supplemental IDE application was necessary prior to implementing the change.

FDA agrees that it will accept and review statistically valid and reliable data and any other information from an investigation that is conducted under section 520(g) of the act, provided that the data or information meets the conditions prescribed in section 515(d)(B)(iii). The comment suggests, however, that the decision about whether the change meets the criteria of sections 515(d)(B)(iii) and 520(g)(6) of the act rests solely with the IDE sponsor. FDA does not agree with this premise. Although section 520(g)(6) of the act states that the sponsor shall determine whether the device/manufacturing or protocol change meets the criteria for submitting a notice for FDA review and acceptance under this provision, the statute does not state that the sponsor determines whether the data resulting from the clinical trial meets the criteria for acceptance or review under section 515(d)(B)(iii) of the act. Consistent with FDA's decisions on all other clearance and approval submissions, the final determination regarding whether the application contains statistically valid and reliable information, in accordance with these sections, rests with FDA.

III. Environmental Impact

The agency has determined under 21 CFR 25.30(h) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

IV. Analysis of Impacts

FDA has examined the impact of this final rule under Executive Order 12866, the Regulatory Flexibility Act (5 U.S.C. 601-612), and the Unfunded Mandates Reform Act of 1995 (2 U.S.C. 1532). Executive Order 12866 directs agencies to assess all costs of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). Unless the head of the agency certifies that the rule would not have a significant economic impact on a substantial number of small entities, the Regulatory Flexibility Act

requires agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities. The Unfunded Mandates Reform Act requires that agencies prepare a written assessment of anticipated costs and benefits before proposing any rule that results in an expenditure of \$100 million or more by State, local, or tribal governments in the aggregate or by the private sector, in any 1 year. The agency believes that this rule is consistent with the regulatory philosophy and principles identified in the Executive Order, and these two statutes.

FDAMA added new section 520(g)(6) of the act to permit certain changes to a device, manufacturing processes, or clinical protocols during the course of a clinical investigation without having to obtain prior FDA approval of a new IDE or an IDE supplement. In addition to specifying the types of changes to clinical studies allowed without prior approval, section 520(g)(6) of the act provides that the sponsor must provide notice within 5 days of making the change, and that the agency define, by regulation, the term "credible information" that the sponsor must use as a basis to decide that the types of changes meet the criteria for implementation without prior FDA approval. This final rule amends existing regulations to implement section 520(g)(6) of the act.

Several comments objected that FDA underestimated the economic effects of the proposed rule and that the proposed requirements were unduly burdensome. These comments generally stated: (1) FDA misinterpreted the statute by requiring 5-day reports for changes that previously were reported in annual reports, thereby making the reporting requirements more burdensome than those under the existing regulation; (2) FDA created an unnecessary burden by requiring IRB approval or DSMB concurrence as "credible information" for protocol changes, and did not take into account in its analysis the costs of requiring IRB approval or DSMB concurrence; (3) FDA created an unnecessary burden by requiring solely design control information as "credible information" for design and manufacturing modifications to a device; (4) FDA should allow 5-working days to mail the notice, instead of 5-calendar days, and (5) the requirements for the contents of a 5-day notice were unduly burdensome by requiring too much detail in the description of the changes.

FDA has adopted most of the comments' suggestions on ways to reduce regulatory burden and provide

flexibility and believes that the resulting final rule is significantly less burdensome and more flexible than the proposed rule. The responses to the comments related to burden are discussed in detail in both sections II and V of this document, but are also described briefly in the following paragraphs.

FDA disagrees with the comment stating the 5-day notice provision should only be used for changes that were previously filed as IDE supplements. FDA believes that the statute clearly requires 5-day notices for some changes that were filed previously as annual reports, but does not believe that this presents any appreciable additional burden on manufacturers. The evidence used to determine whether a change may be made under an annual report or the 5-day notice provision is the same, and in both cases, would need to be generated and evaluated before the change is implemented. Moreover, the regulation should reduce burden by clarifying to sponsors what types of changes require prior approval, thereby eliminating the submission of unnecessary IDE supplements.

FDA agrees with comments that stated there were less burdensome ways of providing credible information for protocol changes than IRB approval or DSMB concurrence. In response to these comments, the final rule has removed IRB approval or DSMB concurrence as a basis for credible information, and instead requires documentation such as peer reviewed published literature, the recommendation of clinical investigator(s), and/or a summary of the data gathered during the clinical trial that supports the sponsor's determination that the change does not affect the rights, safety, or welfare of the subjects. These types of information are already generated and evaluated at the time a sponsor changes a device protocol. Therefore, FDA's definition in the final rule of credible information provides flexibility and negligible additional burden in that it requires the submission of already existing evidence.

FDA also agrees with comments that suggested allowing more flexibility in the credible information required for design changes. In response to comments, the final rule allows information, other than information generated by design controls, to be used as a basis for credible information to support a design change.

FDA also agrees with the suggestion to allow 5-working days to mail the notice, instead of 5-calendar days. This will reduce burden by allowing

sponsors more time to submit the notice.

FDA does not agree with the comment that the contents of the notice were unduly burdensome, and that most of the information should be submitted subsequently in an annual report. The information that is in the notice will have already been generated and evaluated at the time of the change. There is no appreciable burden in submitting information that is already on hand within a 5-day timeframe. Moreover, many comments stated that it was important that FDA advise them, within a short time of the change, if FDA did not believe that the data could be used to support a premarket application. The comment that suggested providing FDA with limited information in the notice would preclude FDA from giving such timely advice.

FDA believes that the revisions in the final rule substantially reduced the regulatory burden. The information that is now required by the final rule as a basis for credible information is the type of information that sponsors should have already generated and evaluated to fulfill their previous reporting requirements under the existing IDE and QS regulations. The only additional burden is the shortened reporting timeframe. As discussed previously, this reporting timeframe should present no appreciable burden because the contents of the submission should have been generated and evaluated before a change is made.

FDA estimates that it will receive 300 5-day reports annually, and that 200 to 300 manufacturers will submit these notices annually. FDA believes that this rule will affect a substantial number of small entities. For the reasons stated previously, however, FDA does not believe that this rule will have a significant impact on a substantial number of small entities. FDA believes that there will be some small additional cost associated with mailing, and training the persons responsible for submissions about the requirements of this rule. FDA believes that training the responsible employees will only take a few hours, and that additional mailing costs are minimal.

Accordingly, the agency certifies that this rule will not have a significant economic impact on a substantial number of small entities. Additionally, this rule does not trigger the requirement for a written statement under section 202(a) of the Unfunded Mandates Reform Act because it does not impose a mandate that results in an expenditure of \$100 million or more by State, local, or tribal governments in the

aggregate or by the private sector, in any 1 year.

V. Paperwork Reduction Act of 1995

This rule contains information collection provisions which are subject to review by OMB under the Paperwork Reduction Act of 1995 (the PRA) (44 U.S.C. 3501-3520). The title, description and respondent description of the information collection provisions are shown below with an estimate of the annual reporting burden. Included in the estimate is the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing each collection of information.

Title: Medical Devices; Investigational Device Exemptions; Supplemental Applications.

Description: Section 201 of FDAMA amended the act by adding new section 520(g)(6) to the act, which permits a sponsor, based on "credible information," as defined by the Secretary, to implement certain changes to an investigational device or to a clinical protocol without prior approval of an IDE supplement if the modifications meet certain criteria and if notice is provided to FDA within 5-working days of making the change. In order to implement this provision, FDA is amending § 812.35(a) to describe which types of changes may be made without prior approval and to describe the credible information to be included in a notice to FDA under this provision.

For developmental or manufacturing changes, sponsors would be required to submit credible information that consists of a summary of the information generated from the design control procedures under § 820.30, preclinical/animal testing, peer reviewed published literature, or other reliable information such as clinical information gathered during the trial or from marketing. For a protocol change, the sponsor must submit credible information that consists of documentation such as peer reviewed published literature, the recommendation of the clinical investigator(s), and/or a summary of the data gathered during the clinical trial which supports the sponsor's determination that the change does not affect the rights, safety, or welfare of the subjects. FDA will review the notices to determine whether they meet the criteria of section 520(g)(6) of the act or whether additional action is necessary to assure the protection of the public health.

Description of Respondents: Businesses or other for profit organizations.

FDA notes that it receives approximately 3,000 supplements annually for changes to IDE's. As discussed in the Analysis of Impacts in section IV of this document, FDA anticipates that it will receive approximately 300 5-day reports annually. In accordance with the statute, which requires that this rule's procedures be established 1 year from the date of enactment of FDAMA, FDA is requiring that all changes in investigational studies, including ongoing studies, that meet the criteria described in this rule, be reported in 5-day notices if those changes are implemented on or after the effective date of this rule.

FDA published the proposed rule (63 FR 38131), submitted the information collection requirements in the proposed rule to the Office of Management and Budget (OMB) for review, and invited interested persons to submit comments on the information collection requirements to OMB. Most comments discussed have an impact, directly or indirectly, on the information collection requirements. FDA has responded to these comments in detail in section II of this document.

Several comments stated that 5-day notices should be submitted only for changes that had been submitted previously in IDE supplements. These comments stated that the requirement of 5-day notices was more burdensome if it was required for changes that had been submitted previously as annual reports.

For the reasons described more fully earlier in this preamble, FDA believes that the language in section 520(g)(6) of the act clearly requires that certain changes that previously were submitted as annual reports now be submitted as 5-day notices. Nonetheless, FDA believes that the final regulation will reduce burden on industry in two ways. First, section 520(g) of the act makes mandatory, FDA's previous practice of allowing certain changes to be implemented by notification to FDA in an annual report. Second, this regulation provides clarification on the types of changes that could be implemented without prior agency approval, thus eliminating the submission of IDE supplements that are not needed.

Finally, FDA believes that the submission of a 5-day report for certain changes that previously were submitted in annual reports will not impose any appreciable additional burden on industry because both the evidence used

to determine whether a change may be made under an annual report and a 5-day notice provision is the same, and would need to be generated and evaluated before the change is implemented. Accordingly, a requirement to send information that is available before the change is made within 5 days of the change, as opposed to a later time after the change, is not an appreciable additional burden.

Several comments stated that the proposed definitions of credible information necessary to support a 5-day notice were unduly burdensome. For design changes, the proposed rule stated that credible information would consist of information generated by design controls. For protocol changes, the proposed rule stated that credible information would consist of approval of an IRB, concurrence of a DSMB, or peer reviewed literature.

Many comments objected to the concurrence of IRB's and DSMB's as credible information because they stated that third party review for changes that previously had not required such review was burdensome. Some of the reasons specifically stated that FDA had not adequately considered the costs to sponsors to obtain this type of review.

In response to these comments, the final rule has eliminated the requirement for IRB approval or DSMB concurrence as evidence of credible information, and instead requires documentation such as peer reviewed published literature, the recommendation of clinical investigator(s), and/or a summary of the data gathered during the clinical trial that supports the sponsor's determination that the change does not affect the rights, safety, or welfare of the subjects. At the time a sponsor changes a device protocol, this type of evidence is already generated and evaluated. Therefore, FDA's definition of credible information in the final rule provides flexibility and negligible additional burden in that it requires the submission of already existing evidence.

Other comments objected to the lack of flexibility in the requirement for credible evidence for design changes. These comments supported the proposal to use information generated by design controls, but stated that FDA should also allow other information. FDA has addressed these concerns in the final rule by allowing other information to be used as a basis for credible information to support a design change.

Some comments requested that FDA allow more time for the submission of reports by allowing reports to be made within 5-working days of the change instead of 5-calendar days. FDA has

stated in the preamble to this final rule that 5-working days from the change is the appropriate timeframe for submissions. This policy should allow sponsors to reduce costs by allowing them additional time to prepare notices.

One comment suggested that the requirements for the contents of a 5-day notice were unduly burdensome in that the statute required a notice and not a detailed description of the changes. The comment further suggested that FDA should require only a notice of the change while the detailed description would be reported in the annual report.

As discussed more fully earlier in the preamble of this document, FDA does not agree with this comment. As modified in the final rule, the information submitted to the agency in the 5-day notice is the same information

that the sponsor would have submitted in the annual report, and therefore, should not represent an increased burden. Moreover, the submission of less information would not allow FDA to notify sponsors that changes require a full supplement until the time of the annual report, and therefore may result in sponsors wasting resources gathering data that ultimately may not be used to support a premarket application.

One comment stated that FDA's estimate of IDE changes that would be submitted each year was underestimated. This comment stated that there were 297 original IDE's filed in 1997 and it was conceivable that as many as 10 changes for each of these original IDE's could occur per year. Based on these figures, the comment stated the estimate should be 2,900

responses, instead of 300 responses stated in the proposed rule. FDA does not agree with these estimates. FDA receives approximately three supplemental filings per original submission per year. One of these submissions should always be an annual progress report. Only a small subset of the two remaining submissions, which FDA estimates as 300 for reasons described herein, would be types of changes reported in 5-day notices.

One comment stated that the annual reporting burden in the proposed rule did not take into consideration ongoing studies. FDA did take such ongoing studies into account in arriving at the estimates reported.

FDA estimates the burden for this collection of information as follows:

TABLE 1.—ESTIMATED ANNUAL REPORTING BURDEN¹

21 CFR Section	No. of Respondents	Annual Frequency per Response	Total Annual Responses	Hours per Response	Total Hours
812.35(a)(3)	300	1	300	10	3,000

¹ There are no capital costs or operating and maintenance costs associated with this collection of information.

Based upon a review of IDE's submitted in recent years, FDA estimates that approximately 300 notices of IDE changes will be submitted each year. Of these IDE changes, FDA estimates that 100 of these changes were previously submitted as supplements and 200 of these changes would have been submitted in annual reports. Based upon discussions with sponsors of IDE's and FDA's own experience in reviewing these types of documents, FDA estimates that it will take approximately 10 hours for a sponsor to prepare a notice of IDE change. Although this was the estimate offered in the proposed rule, FDA received comments indicating that the burden hours in the proposal were underestimated. As a result of the changes made in this final rule, the burden has decreased significantly. Thus, FDA believes that the estimate of 10 hours per submission is now accurate. FDA therefore estimates that the total annual burden for preparation of these notices will be 3,000 hours.

The information collection provisions of this final rule have been submitted to OMB for review.

Prior to the effective date of this final rule, FDA will publish a document in the **Federal Register** announcing OMB's decision to approve, modify, or disapprove the information collection provisions in this final rule. An agency may not conduct or sponsor, and a person is not required to respond to, a

collection of information unless it displays a currently valid OMB control number.

List of Subjects in 21 CFR Part 812

Health records, Medical devices, Medical research, Reporting and recordkeeping requirements.

Therefore, under the Federal Food, Drug, and Cosmetic Act, and, under authority delegated to the Commissioner of Food and Drugs, 21 CFR part 812 is amended as follows:

PART 812—INVESTIGATIONAL DEVICE EXEMPTIONS

1. The authority citation for 21 CFR part 812 continues to read as follows:

Authority: 21 U.S.C. 331, 351, 352, 353, 355, 357, 360, 360c–360f, 360h–360j, 371, 372, 374, 379e, 381, 382, 383; 42 U.S.C. 216, 241, 262, 263b–263n.

2. Section 812.35 is amended by revising paragraph (a) to read as follows:

§ 812.35 Supplemental applications.

(a) *Changes in investigational plan—*(1) *Changes requiring prior approval.* Except as described in paragraphs (a)(2) through (a)(4) of this section, a sponsor must obtain approval of a supplemental application under § 812.30(a), and IRB approval when appropriate (see §§ 56.110 and 56.111 of this chapter), prior to implementing a change to an investigational plan. If a sponsor intends to conduct an investigation that

involves an exception to informed consent under § 50.24 of this chapter, the sponsor shall submit a separate investigational device exemption (IDE) application in accordance with § 812.20(a).

(2) *Changes effected for emergency use.* The requirements of paragraph (a)(1) of this section regarding FDA approval of a supplement do not apply in the case of a deviation from the investigational plan to protect the life or physical well-being of a subject in an emergency. Such deviation shall be reported to FDA within 5-working days after the sponsor learns of it (see § 812.150(a)(4)).

(3) *Changes effected with notice to FDA within 5 days.* A sponsor may make certain changes without prior approval of a supplemental application under paragraph (a)(1) of this section if the sponsor determines that these changes meet the criteria described in paragraphs (a)(3)(i) and (a)(3)(ii) of this section, on the basis of credible information defined in paragraph (a)(3)(iii) of this section, and the sponsor provides notice to FDA within 5-working days of making these changes.

(i) *Developmental changes.* The requirements in paragraph (a)(1) of this section regarding FDA approval of a supplement do not apply to developmental changes in the device (including manufacturing changes) that do not constitute a significant change in

design or basic principles of operation and that are made in response to information gathered during the course of an investigation.

(ii) *Changes to clinical protocol.* The requirements in paragraph (a)(1) of this section regarding FDA approval of a supplement do not apply to changes to clinical protocols that do not affect:

(A) The validity of the data or information resulting from the completion of the approved protocol, or the relationship of likely patient risk to benefit relied upon to approve the protocol;

(B) The scientific soundness of the investigational plan; or

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

(iii) *Definition of credible information.* (A) Credible information to support developmental changes in the device (including manufacturing changes) includes data generated under the design control procedures of § 820.30, preclinical/animal testing, peer reviewed published literature, or other reliable information such as clinical information gathered during a trial or marketing.

(B) Credible information to support changes to clinical protocols is defined as the sponsor's documentation supporting the conclusion that a change does not have a significant impact on the study design or planned statistical analysis, and that the change does not affect the rights, safety, or welfare of the subjects. Documentation shall include information such as peer reviewed published literature, the recommendation of the clinical investigator(s), and/or the data gathered during the clinical trial or marketing.

(iv) *Notice of IDE change.* Changes meeting the criteria in paragraphs (a)(3)(i) and (a)(3)(ii) of this section that are supported by credible information as defined in paragraph (a)(3)(iii) of this section may be made without prior FDA approval if the sponsor submits a notice of the change to the IDE not later than 5-working days after making the change. Changes to devices are deemed to occur on the date the device, manufactured incorporating the design or manufacturing change, is distributed to the investigator(s). Changes to a clinical protocol are deemed to occur when a clinical investigator is notified by the sponsor that the change should be implemented in the protocol or, for sponsor-investigator studies, when a sponsor-investigator incorporates the change in the protocol. Such notices shall be identified as a "notice of IDE change."

(A) For a developmental or manufacturing change to the device, the notice shall include a summary of the relevant information gathered during the course of the investigation upon which the change was based; a description of the change to the device or manufacturing process (cross-referenced to the appropriate sections of the original device description or manufacturing process); and, if design controls were used to assess the change, a statement that no new risks were identified by appropriate risk analysis and that the verification and validation testing, as appropriate, demonstrated that the design outputs met the design input requirements. If another method of assessment was used, the notice shall include a summary of the information which served as the credible information supporting the change.

(B) For a protocol change, the notice shall include a description of the change (cross-referenced to the appropriate sections of the original protocol); an assessment supporting the conclusion that the change does not have a significant impact on the study design or planned statistical analysis; and a summary of the information that served as the credible information supporting the sponsor's determination that the change does not affect the rights, safety, or welfare of the subjects.

(4) *Changes submitted in annual report.* The requirements of paragraph (a)(1) of this section do not apply to minor changes to the purpose of the study, risk analysis, monitoring procedures, labeling, informed consent materials, and IRB information that do not affect:

(i) The validity of the data or information resulting from the completion of the approved protocol, or the relationship of likely patient risk to benefit relied upon to approve the protocol;

(ii) The scientific soundness of the investigational plan; or

(iii) The rights, safety, or welfare of the human subjects involved in the investigation. Such changes shall be reported in the annual progress report for the IDE, under § 812.150(b)(5).

* * * * *

Dated: October 27, 1998.

William B. Schultz,

Deputy Commissioner for Policy.

[FR Doc. 98-31245 Filed 11-20-98; 8:45 am]

BILLING CODE 4160-01-F

DEPARTMENT OF STATE

22 CFR Part 40

[Public Notice 2910]

Visas: Grounds of Ineligibility

AGENCY: Bureau of Consular Affairs, Department of State.

ACTION: Final rule.

SUMMARY: This rule finalizes the interim rule published December 29 1997 (62 FR 67564) and implements sections of the Illegal Immigration Reform and Immigrant Responsibility Act of 1996 (IIRIRA). IIRIRA added new grounds of inadmissibility for: certain aliens who have not been inoculated against infectious diseases designated by statute or by the Advisory Committee for Immunization Practices (ACIP); aliens who have been subject to certain civil penalties; alien student visa abusers; aliens present in the United States without admission or parole; aliens who fail to attend removal proceedings; unlawful alien voters; and former citizens who renounced United States citizenship in order to avoid paying taxes. Some of these sections also provide for waivers of grounds of inadmissibility. The rule also incorporates in the Department's regulations a delegation of authority from the Immigration and Naturalization Service pertaining to waivers of inadmissibility under the Immigration and Nationality Act. Finally, the rule makes a technical correction. Generally, these rules are necessary to ensure that consular officers properly enforce the above-mentioned grounds of ineligibility when adjudicating visa applications.

EFFECTIVE DATES: The effective dates are as follows: for §§ 40.11, 40.52, 40.66, 40.104, and 40.105 the effective date is September 30, 1996; for § 40.67 the effective date is November 30, 1996; for §§ 40.61, 40.62, 40.91, 40.92, 40.93, the effective date is April 1, 1997; and for § 40.22, the effective date is September 30, 1997.

FOR FURTHER INFORMATION CONTACT: H. Edward Odom, Chief, Legislation and Regulations Division, Visa Office, Room L603-C, SA-1, Washington, DC 20520-0106 (odomhe@sa1wpoa.us-state.gov).

SUPPLEMENTARY INFORMATION: The Department published an interim rule, Public Notice 2666 at 62 FR 67564, December 29, 1997, with a request for comments, for numerous sections of Title 22, Part 40 of the Code of the Federal Regulations. The rules were primarily proposed to implement provisions of the Illegal Immigration