H. Electronic Filing of Data

The Department currently accepts data submissions either in paper form or on magnetic disk or tape. Most large carriers submit the bulk of their data on magnetic media, with large data submissions, such as the Passenger Origin-Destination Survey and T–100 market reports nearly universally submitted on tape or cassette. Electronic submission of data can be processed more quickly, and at lower cost, than similar data submitted in paper form.

The Department now accepts the official filing of international fare and fare rules tariffs electronically (See 14 CFR Part 221 and 61 FR 18070–18075, April 24, 1996). Given the Department's limited resources, it would be impossible to process the volume of tariff data received if these data were filed in a wholly paper environment. Similarly, the Department is increasingly burdened by the filing of required financial and traffic data in paper form.

We request that respondents provide specific comments on the following matters:

[H–1] All air carriers who supply aviation data to the Department are requested to comment on their ability to file data electronically or on magnetic media, i.e., via tape or disk, or over the Internet.

[H–2] If certain large database material now accepted by the Department in electronic form (e.g., the T–100/T–100(f), Origin-Destination Survey, and 298–C reports) are submitted on paper, relevant carrier respondents are requested to indicate why magnetic media are not employed for their submissions.

Contact Persons

We recognize that formal comments submitted to the Department on rulemaking matters are usually submitted by corporate counsel. However, we are seeking comments regarding complex technical issues in anticipation of a formal rulemaking, in areas which are generally outside the area of expertise of legal counsel. It would aid in our evaluation of any technical comments to be able to contact persons with direct knowledge of technical issues being commented upon. Respondents are urged to supply the names, telephone numbers, and addresses of knowledgeable individuals who can be contacted for a more detailed discussion of any technical matters that the respondent counsel cannot answer directly. There may be multiple contact persons for any particular item, or in total. These contact persons should be listed on the last page of any submitted filing, along with their area(s) of expertise.

Regulatory Process Matters

Executive Orders 12612 and 12866

The Department has determined that the proposed notice of proposed rulemaking is not a significant regulatory action under Executive Order 12866. However, the proposed rule may be significant under the Department's Regulatory Policies and Procedures (44 CFR 11304), because of substantial industry interest and because it may result in a reduction in paperwork and filing burden for U.S. carriers. The Department has also analyzed the proposal in accordance with the principles and criteria contained in Executive Order 12612 (''Federalism''), and has determined that the rule does not have sufficient federalism implications to warrant the preparation of a Federalism Assessment. This rule would not impose unfunded mandates as defined by the Unfunded Mandates Reform Act of 1995.

Regulatory Flexibility Act

The Regulatory Flexibility Act of 1980, 5 U.S.C. 601 et seq., was enacted by Congress to ensure that small entities are not unnecessarily and disproportionately burdened by government regulations. The Act requires agencies to review proposed regulations that may have a significant economic impact on a substantial number of small entities. For purposes of this notice, small entities include air taxis, commuter air carriers, and smaller U.S. and foreign airlines.

Although we do not believe the existing rule imposes a significant economic impact on a substantial number of small entities, it does affect many small entities. For that reason, we specifically seek public comment on what steps we can take to lessen or eliminate any burdens it imposes on small entities.

Paperwork Reduction Act

Our current rules contain significant collection-of-information requirements. Changes we may propose will be subject to the Paperwork Reduction Act, Public Law No. 96–411, 44 U.S.C. Chapter 35. The revised rules are expected to result in a net paperwork reduction for the industry.

Regulation Identifier Number

A regulation identifier number (RIN) is assigned to each regulatory action listed in the Unified Agenda of Federal Regulations. The Regulatory Information Service Center publishes the Unified Agenda in April and October of each year. The RIN number contained in the heading of this document can be used to cross reference this action with the Unified Agenda.

Patrick V. Murphy,

Deputy Assistant Secretary for Aviation International Affairs.

Robert A. Knisely,

Acting Director, Bureau of Transportation Statistics.

[FR Doc. 98–18855 Filed 7–14–98; 8:45 am]

BILLING CODE 4910–62–P

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: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is proposing to amend the Investigational Device Exemptions (IDE) regulation. The proposed 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 proposed rule also defines the credible information to be used by sponsors to determine if the criteria are met.

DATES: Submit written comments on or before September 28, 1998. Written comments on the information collection provisions should be submitted by August 14, 1998.

ADDRESSES: Submit written comments on the proposed rule to the Documents Management Branch (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Submit written comments on the information collection requirements to the Office of Information and Regulatory Affairs, OMB, New Executive Office Bldg., 725 17th St. NW., rm. 10235, Washington, DC 20503, Attn: Desk Officer for FDA.

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.

Currently, § 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(g)(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 current IDE regulation and the new statute 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 § 812.35(a).

Section 520(g)(6) of the act, which is a result of the new law, 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), 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.

To implement new section 520(g)(6), FDA is proposing to amend § 812.35(a) to permit changes to the investigational device, including manufacturing changes, or to the clinical protocol, in accordance with the statutory criteria. This proposed rule also implements the 5 day notice requirement and defines the credible information to be used by sponsors to determine if the statutory criteria are met. The agency is soliciting comments on the proposal and, in particular, on the definition of credible information. Finally, the amended regulation codifies existing agency practice regarding the types of changes that could be made to other parts of the investigational plan (i.e., other than changes to the device or clinical protocol) and be reported in the annual progress report without prior agency approval.

II. Discussion of Proposed Amendments

The proposed rule amends part 812 by revising § 812.35(a) to track the new statutory language and to define the credible information to be used by IDE sponsors to determine if the statutory criteria are met. This proposal consists of the following provisions:

A. Changes Requiring Prior Approval

Proposed § 812.35(a)(1) requires that changes to the investigational plan, except as provided for in proposed § 812.35(a)(2) through (a)(4), be approved by FDA and the IRB, as applicable under §§ 56.110 and 56.111 (21 CFR 56.110 and 56.111), before being implemented. In addition, this section continues to require an IDE sponsor who intends to conduct an investigation that involves an exception to informed consent under § 50.24 (21 CFR 50.24) to submit a new IDE application rather than an IDE supplement.

B. Changes Effected for Emergency Use

Proposed § 812.35(a)(2), which parallels the existing regulation, addresses deviations from the investigational plan to protect the life or physical well-being of a subject in an emergency. Such deviations would not require prior FDA approval but must be reported to the agency by the sponsor within 5 working days of when the sponsor learns of the deviation. A detailed discussion of this provision was provided in the guidance document entitled, ''Guidance for the Emergency Use of Unapproved Medical Devices'' (50 FR 42866, October 22, 1985).

C. Changes Effected With Notice to FDA Within 5 Days

Proposed § 812.35(a)(3) describes the statutory criteria under which developmental changes to the investigational device, including manufacturing changes, and changes to the clinical protocol may be made without prior approval by FDA. As stated in section 520(g)(6) of the act, developmental changes to the device or manufacturing process may be made if the changes do not constitute a significant change in design or basic principles of operation and are made in response to information gathered during the course of the investigation.

Changes to the clinical protocol may be made if the modifications do not affect the validity of the data or information resulting from the study, the likely risk to benefit relationship that was used to approve the protocol, the scientific soundness of the investigational plan, or the rights, safety, or welfare of the subjects in the trial. As noted previously, the current IDE regulation allows sponsors to modify the investigational plan without prior agency approval if the

modification does not affect the scientific soundness of the plan or the rights, safety, or welfare of the subjects. The new statute specifies that, in addition to these criteria, IDE sponsors who change the clinical protocol must also consider the impact that the change may have on the validity of the data resulting from the study and the risk to benefit relationship that was used to approve the protocol. FDA believes that these additional criteria are consistent with the agency's general criteria under the current regulation that provide that changes may be made to the investigational plan as long as such changes ensure the protection of patient safety and rights and the integrity of the clinical trial.

D. Definition of Credible Information

To help sponsors decide if the criteria set forth in section 520(g)(6) of the act have been met, and in accordance with FDAMA, the agency is defining what it would consider to be credible information to support a decision by the sponsor that prior agency approval for a proposed change to a device, manufacturing process, or protocol is not required and that a notice within 5 days of effecting a change will be sufficient. As described in the following paragraph, FDA believes that the definition of credible information will be different depending upon whether the sponsor is modifying the device (or manufacturing process) or the clinical protocol.

1. Device and Manufacturing Changes

For changes to the device, including manufacturing changes, FDA believes that the data generated by design control procedures during the device development process will help manufacturers distinguish those changes that could be implemented without prior approval from those that would require approval. Under § 812.1(a) (21 CFR 812.1(a)), manufacturers of investigational devices are exempt from the good manufacturing practice (GMP) requirements of section 520(f) of the act, except for the design control procedure requirements (§ 820.30 (21 CFR 820.30)), if applicable. Design control procedures consist of a system of inter-related checks and balances that make the systematic assessment of design an integral part of the device development process. Under the design-control section of the quality system regulation, manufacturers are required to have in place a systematic set of requirements and activities for the management of design and development, including documentation of design inputs, appropriate risk analysis, design output, test procedures, verification and validation procedures, and documentation of formal design reviews. Use of design controls in the development process for medical devices contributes to the protection of the public in general, as well as of patients involved in clinical trials, from potentially unsafe devices. By using the information generated by design controls, IDE sponsors are able to assess the potential impact of changes in the device design or manufacturing process prior to implementing them in their clinical investigations.

Under the new law and this proposed implementing regulation, certain developmental changes to the investigational device (including manufacturing changes), which are made in response to information gathered during the course of the investigation, are eligible for implementation without prior agency approval. Modifications that constitute a significant change in design or basic principles of operation, however, may not be made without prior approval of an IDE supplement. Through the data generated by the appropriate risk analysis and the subsequent verification and validation testing done as a part of the design control process, sponsors should be able to judge whether a change to the device would constitute a significant change in design or one that changes the basic principles of operation. The agency believes that any change that could significantly affect the safety and/or effectiveness of the device is a significant change. FDA also believes that any change to the basic principles of operation of a device would be highly likely to constitute a significant change; however, the agency is soliciting comments on this premise.

In determining whether a change to the design of the device would be considered significant and require agency approval prior to implementation, FDA is proposing that IDE sponsors rely upon information generated by design controls to supply the credible information that would be the basis of that decision. Specifically, the manufacturer should conduct an appropriate risk analysis, followed by verification and validation testing, as required by design control procedures. If it is determined that no new types of risks are introduced by the change and that the subsequent testing demonstrates that the design outputs meet the design input requirements, then the change could be made without prior agency approval, if the sponsor notifies FDA within 5 days of implementation. If, however, the risk analysis identifies new types of risks, the verification/validation testing indicates that the design input requirements are no longer satisfied, or the design input requirements need to be modified, then the change would require prior approval.

As an example, consider a change in material from polyvinylchloride (PVC) to silicone in a catheter. In accordance with design control procedures, the manufacturer would conduct the appropriate risk analysis. Assuming that the risk analysis did not identify any new types of risks for this device compared to the unmodified device, then the manufacturer would proceed to conduct the verification and validation testing. As a part of these activities, the manufacturer should also 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 for this device. If the results of the testing demonstrate that all of the risks (those identified in the risk analysis and those identified by the agency in its previous correspondence to the firm) have been adequately addressed and that the design output meets the design input requirements, then the change could be implemented without prior FDA approval. Alternatively, if the manufacturer had proposed a change from PVC to latex, the risk analysis should have indicated a new type of risk, e.g., possible latex sensitivity. In this case, the change should not be made without prior FDA review and approval.

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

By using the data generated by design control procedures, the manufacturer should be able to identify significant changes to the investigational device or manufacturing process, i.e., those that introduce new types of risks or cause

the design outputs to no longer meet the design input requirements. In the guidance document entitled, ''Deciding When to Submit a 510(k) for a Change to an Existing Device,'' the agency has identified generic types of device and manufacturing modifications. The previous guidance may be found on the World Wide Web at ''http://www.fda.gov/cdrh''. Although this guidance applies to modifications of marketed devices, the types of changes identified in the document are also applicable to investigational devices. These include changes to the control mechanism, principle of operation, energy type, environmental specifications, performance specifications, ergonomics of patient-user interface, dimensional specifications, software or firmware, packaging or expiration dating, sterilization, and the manufacturing process (including the manufacturing site). Such changes can range from minor to significant, depending upon the particular device, the type of modification, and the extent of the modification. As discussed previously, significant changes of any of the previous types would not be eligible for the 5 day notice provision, but rather would require prior FDA approval.

2. Protocol Changes

The new statute also permits changes to the clinical protocol to be made and reported within 5 days of implementation if the changes do not affect the validity of the data or information that will result from the clinical trial, the likely patient risk to benefit relationship used to approve the study, the scientific soundness of the investigational plan, or the rights, safety, or welfare of the subjects. FDA is proposing that the credible information relied upon to support this change should consist of a statistical analysis performed by the sponsor and independent confirmation by the IRB chairperson, the data safety monitoring board (DSMB), or published literature. For a modification to be eligible for implementation under this provision, FDA believes the IDE sponsor should conduct an assessment of the impact of the proposed change on the study design and planned statistical analysis and determine that they would not be adversely affected. In addition to this assessment, FDA is proposing that the credible information that is the basis of the sponsor's determination include approval by the IRB chairperson (or designee) or concurrence of the DSMB. For certain types of changes, peer reviewed published literature also could be the additional credible evidence to support a protocol modification. Generally, FDA would rely upon the IRB chairperson to review changes that are related to the rights, safety, or welfare of the subjects in the trial, while the approval/recommendation of the DSMB or the peer reviewed published literature would be relied upon for changes that are related to the scientific soundness of the investigational plan or validity of the data. Several examples of these types of changes are provided as follows.

1. Increasing the frequency at which data or information is gathered or lengthening the subject follow-up period. Assuming that the sponsor's assessment of the impact of the proposed change on the study design and planned statistical analysis demonstrates that they would not be adversely affected, FDA believes this type of modification could be implemented without agency approval if the IRB chairperson agrees that the rights, safety, and welfare of the subjects would not be affected.

2. Modifying the protocol to include additional patient observations/measurements or modifying the inclusion/exclusion criteria to better define the target patient population. After confirming that the proposed change would not have a significant impact on the study design or planned statistical analysis, this type of change could be implemented if the DSMB either recommends the change or approves it. Approval by the IRB chairperson or peer reviewed published literature that supports the change may be substituted for the DSMB's concurrence, depending upon the extent of these types of changes.

3. Increasing the number of investigational sites or number of subjects to be enrolled in the study. Again, after determining that the proposed change would not have a significant impact on the study design or planned statistical analysis, the sponsor could increase the number of investigational sites or subjects in the trial if the DSMB overseeing the clinical investigation either recommends or concurs with the study expansion. If such a change to the protocol is implemented, however, IDE sponsors are reminded that the study, as expanded, would need to be completed before the marketing application could be submitted. Furthermore, under 21 CFR 812.7(c), sponsors are prohibited from unduly prolonging a clinical investigation, i.e., commercializing an investigational device. Therefore, sponsors should ensure that the study expansion is well justified.

4. Modifying the secondary endpoint(s). Following the assessment of the impact of the proposed change on the study design and planned statistical analysis, the secondary endpoint(s) could be modified if the DSMB or peer reviewed published literature supports the change. For example, eliminating the assessment of post-void residuals in a benign prostatic hyperplasia (BPH) study could be implemented if peer review published literature supported the change, i.e., if the literature indicated that this is not a significant outcome measure for the intervention being studied.

Alternatively, FDA believes that the following types of protocol modifications would not generally be eligible for implementation without prior agency approval because they are likely to have a significant effect on the validity of the data resulting from the trial and/or on the scientific soundness of the trial design:

- Change in indication
- Change in type or nature of study control
- Change in the primary endpoint variable
- Change in the method of statistical evaluation
- Early termination of the study (except for reasons related to patient safety)

E. Notice of IDE Change

Proposed § 812.35(a)(3)(iv) would require IDE sponsors who have determined, based on the credible evidence as defined by FDA, that changes to their device and/or clinical protocol do not require prior agency approval to notify the agency within 5 days of making the change. To be in compliance with this requirement, sponsors would be required to submit the notice within 5-calendar days of the date the device, incorporating the change, is first distributed to the investigator(s). For protocol changes, the notice would need to be submitted within 5-calendar days of the sponsor's notification to the clinical investigators that the protocol has been modified or, for sponsor-investigator studies, within 5-calendar days of when the sponsor-investigator incorporates the protocol change. In addition, proposed § 812.35(a)(3)(iv) states that the notification shall be identified as a ''Notice of IDE Change.'' FDA is proposing to require that the notices be identified in this manner so that they can be easily distinguished from IDE supplements being submitted for agency approval.

This proposed section of the regulation also describes the

information to be included in the notice. For a device or manufacturing change, FDA is proposing that the notice include: (1) A summary of the relevant information gathered during the course of the investigation upon which the change was based; (2) a description of the change that has been made to the device or manufacturing process, including a cross-reference to appropriate sections of the original device description or manufacturing process; and (3) a statement that no new risks were identified by the appropriate design control risk analysis and that the verification/validation testing demonstrated that the design outputs met the design input requirements. For a protocol change, FDA is proposing that the notice include: (1) A description of the change that has been made to the clinical protocol, including a cross-reference to appropriate sections of the original protocol, and (2) an assessment supporting the conclusion that the change does not have a significant impact on the study design or planned statistical analysis of safety and effectiveness. As discussed in the previous section, protocol changes that relate to the rights, safety, or welfare of the subjects would be required to be supported by a letter from the IRB chairperson (or designee) stating that the change is acceptable. Protocol changes that relate to the scientific soundness of the investigational plan or validity of the data would require the support of a data safety monitoring board overseeing the investigation or peer reviewed published literature, as appropriate.

F. Review of the Notices

Under proposed § 812.35(a)(3), it is the sponsor's responsibility to determine if a change made to the device or the manufacturing process would affect the safety and effectiveness of the device and thus would be considered a significant change requiring prior agency approval. Similarly, the sponsor must decide if a change to the clinical protocol would affect the validity of the data resulting from the clinical trial, the likely risk to benefit relationship relied upon to approve the study, the scientific soundness of the investigational plan, or the rights, safety, or welfare of the subjects. Under proposed § 812.35(a)(3)(iii), the agency has defined the type of credible information IDE sponsors should use in determining if the change meets the statutory criteria.

Under proposed § 812.35(a)(3)(v), however, FDA reserves the right to question the sponsor's determination that the change met the statutory criteria. Thus, if the agency has reason to believe, based on the information submitted in the Notice of IDE Change or on other available information, such as reports of adverse events, that the modification did not meet the criteria, FDA will notify the sponsor that the change should have been reviewed and approved before being implemented. Upon receipt of such a communication from FDA, the sponsor would have the option of suspending the investigation until approval is obtained for the change or of reverting to the unmodified device, manufacturing process, or protocol. FDA recognizes the potential impact that this action could have on the IDE sponsor and the clinical trial and, therefore, intends to take such action only if the agency determines that the modification to the device, manufacturing process, or clinical protocol could jeopardize patient safety, the scientific soundness of the investigation, or the validity of the data resulting from the trial. Such determinations would be made by the individuals authorized to approve IDE's.

G. Changes Submitted in the Annual Report

Under proposed § 812.35(a)(4), changes to certain portions of the investigational plan other than to the device, manufacturing process, or clinical protocol may continue to be submitted in an IDE annual report under § 812.150(b)(5). Changes to the purpose of the study, the risk analysis, monitoring procedures, labeling for the investigational device, informed consent materials, and IRB information may continue to be submitted in an IDE annual report if the changes do not affect the validity of the data/information resulting from the trial, the risk to benefit relationship relied upon to approve the protocol, the scientific soundness of the investigational plan, or the rights, safety, or welfare of the subjects. The types of changes that would normally satisfy these criteria would be those that would serve to increase patient safety, e.g., clarifying the instructions for use, providing additional information in the informed consent document, or enhancing the monitoring procedures.

Each of the following parts of the investigational plan is discussed as follows and specific examples are provided to illustrate the types of changes that would usually be considered appropriate for submission in an annual report.

1. *Purpose.* Under § 812.25(a), the purpose of the study includes the name and intended use of the device as well as the objectives and duration of the investigation. Examples of changes that may be made to this section of the investigational plan and reported in the annual report include:

- *Changes to the name of the device.* This type of change can be made provided that the new name does not imply a new intended use. Name changes that are made in conjunction with a modification to the device, however, should be submitted either as an IDE supplement or as a notice within 5 days of implementation, as appropriate for the device modification.
- *Clarifications to the intended use of the device.* Such changes may be made if the modifications do not implicitly or explicitly affect the intended use.
- *Minor modifications to the study objectives.* Such changes include clarifying the study objectives as long as the intent of the objectives and the study endpoints are not changed. Study objectives related to future labeling claims for the device may be added under the annual report requirements if the change is minor, as described in proposed § 812.35(a)(4). If, however, the change in the objectives requires protocol modifications, the change should be submitted as an IDE supplement or a notice within 5 days of implementation, as appropriate for the protocol modification.
- *Changes in the duration of the investigation.* If the investigation will take less time or more time to complete than was anticipated at the time the IDE application was submitted, this information may be submitted in the annual report.

2. *Risk Analysis.* If information to be added to the risk analysis does not affect the risk to benefit relationship, it may be reported in the annual report. For example, modifying the risk analysis to include foreign data that confirms the original patient risk to benefit relationship could be submitted in the annual report. If, however, during the course of the investigation, the sponsor becomes aware of information that may adversely affect the risk analysis, this information should be submitted as a supplement under § 812.35 indicating that the risk to benefit relationship has changed.

3. *Monitoring Procedures.* A change in the name and/or address of the monitor may be submitted in the annual report. In addition, changes in the monitoring procedures that are consistent with the ''Guideline for the Monitoring of Clinical Investigations'' are eligible for this type of reporting mechanism.

4. *Labeling.* Labeling changes that clarify the instructions for use or serve to increase subject safety may be

implemented without prior agency approval and submitted in the annual report. Adding contraindications, hazards, adverse effects, interfering substances/devices, warnings, or precautions to the labeling, however, may require concomitant changes to the protocol (e.g., modifications to the exclusion criteria) and should be submitted in an IDE supplement or notice within 5 days of implementation, as appropriate for the protocol modification.

5. *Informed Consent*. Revisions to the informed consent materials may be made without prior approval and submitted in the annual report if the changes are, for example, to include preliminary results from the trial (if in agreement with expected outcome(s)), clarify the risks and/or potential benefits of the investigational device, or clarify the procedures/tests to which the subjects may be subject.

6. *IRB Information*. A change in the IRB chairperson or address may be reported in the annual report. Changes in approval status of the study, however, must be reported to FDA, all reviewing IRB's, and participating investigators in accordance with § 812.150(b)(2).

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 proposed rule under Executive Order 12866 and the Regulatory Flexibility Act (5 U.S.C. 601–612) (as amended by subtitle D of the Small Business Regulatory Fairness Act of 1996 (Pub. L. 104–121)), and the Unfunded Mandates Reform Act of 1995 (Pub. L. 104–4). 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). The agency believes that this proposed rule is consistent with the regulatory philosophy and principles identified in the Executive Order. This proposed rule has been determinated to be a significant regulatory action as defined by the Executive Order and so is subject to review under the Executive Order.

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. This proposed rule amends existing regulations to implement section 520(g)(6) of the act.

FDAMA added new section 520(g)(6) 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) 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.

Under the existing regulations and policy, §§ 812.35 and 812.150(b)(5), a sponsor is allowed to make certain changes in its investigational device or protocol without prior FDA approval, provided that such changes are reported in an annual progress report. Under the proposed regulation, such changes would be reported in a 5 day notice report, instead of an annual report. Accordingly, the proposed regulation does not require industry to submit a new type of report because a change in a device or protocol triggers a reporting requirement under both the existing and proposed regulation.

FDA's interpretation of the types of changes that are allowed without prior approval in annual reports under the existing regulation, and the proposed regulation's criteria to allow changes without prior approval in 5-day notice reports are consistent. Accordingly, the criteria stated in the proposed regulation does not affect the types of changes that sponsors will be allowed to implement without prior approval, and, therefore, would not add any additional burden to industry.

The kind of credible information that the proposed regulation would require as a basis to determine that a change can be made without prior FDA approval is either currently required under existing regulations, or will not add additional costs. The proposed regulation provides that the type of credible information depends on the type of change.

For design and manufacturing changes, the proposed regulation provides that credible information must be information generated by design controls. The generation of this information currently is required under §§ 812.1 and 820.30. Moreover, this type of information is already required to be submitted in annual progress reports. Under the current regulation, sponsors provide testing data to support the device change. Under the proposed regulation, sponsors are allowed to provide summary information generated by design control procedures. Therefore, sponsors will be able under the proposed regulation to provide less detailed testing information than currently provided in annual progress reports. Accordingly, the proposed regulation's definition of credible information that must be used as a basis to file a 5 day notice does not add any additional burden to industry.

For clinical protocol type changes, the proposed regulation provides that credible information consists of an assessment of the impact of the change on the study design and planned statistical analysis, and approval from the IRB chairperson, a recommendation or concurrence from a DSMB, or published literature that supports the change. The proposed regulation's requirement for an assessment of the impact of the change on the study design and planned statistical analysis is consistent with the analysis performed by sponsors under the current regulation when assessing whether their protocol modification does not affect the scientific soundness. Consultation with an IRB and a DSMB is customary for protocol modifications. Under current regulatory authority, sponsors must report changes to the IRB. *See* 21 CFR 56.108(a)(3), 56.110(b)(2), 812.40 and 812.150(b)(5). Since the current regulations already require that information relating to the study would be generated and provided to IRB's, the generation of this information under the proposed regulation does not add any add additional costs. Although the proposed regulation would add the requirement of IRB chairperson approval, or DSMB recommendation or concurrence, these entities are not paid by the sponsors, and would not generate additional costs.

Similarly, the proposed regulation's requirement for providing FDA with published literature supporting a change does not add additional costs. Under § 812.27(b), sponsors are currently required to submit all publications, whether adverse or supportive, in an IDE application. Supporting publications for changes after approval of an IDE application are submitted in

an annual progress report under § 812.150(b)(5).

The only additional burden posed by the proposed rule would be the timing of the submission. Section 520(g)(6) of the act, as added by FDAMA, requires that the sponsor submit a notice within 5 days of the change. As stated previously, the type of information in the 5 day notice in the proposed regulation would be submitted annually in a progress report under the current regulatory authority. FDA believes that the additional cost of submitting information on each change when that change is made, is not significantly greater than compiling the information and sending it in one annual report. The primary additional costs will be minimal mailing costs.

For the reasons stated previously, the Commissioner of Food and Drugs certifies that this proposed rule will not have a significant economic impact on a substantial number of small entities. Additionally, this proposed 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 proposed 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). A description of these provisions is given 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.

FDA invites comments on: (1) Whether the proposed collection of information is necessary for the proper performance of FDA's functions, including whether the information will have practical utility; (2) the accuracy of FDA's estimate of the burden of the proposed collection of information, including the validity of the methodology and assumptions used; (3) ways to enhance the quality, utility, and clarity of the information to be collected; and (4) ways to minimize the burden of the collection of information on respondents, including through the use of automated collection techniques, when appropriate, and other forms of information technology.

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 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 days of making the change. In order to implement this provision, FDA is proposing to amend § 812.35(a) to describe which types of changes may be made without prior approval and to describe the information to be included in a notice to FDA if this provision is to be exercised. For developmental or manufacturing changes, sponsors would be required to submit a summary of the information from the study upon which the change was based, a description of the change, and a statement that no new risks were identified and that the device testing demonstrated that the design outputs met the design input requirements. For a protocol change, the sponsor must submit a description of the change, an assessment of the impact of the change, and supporting documentation from the IRB chairperson, data safety monitoring board, or peer reviewed published literature, as appropriate. 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 estimates the burden for this collection of information as follows:

TABLE 1.—ESTIMATED ANNUAL REPORTING BURDEN[1]

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 of these notices of IDE changes will be submitted each year. 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. Therefore, FDA estimates that the total annual burden for preparation of these notices will be 3,000 hours.

As required by section 3507(d) of the Paperwork Reduction Act of 1995 (44 U.S.C. 3507(d)), the agency has submitted the information collection provisions of this proposed rule to OMB for review. Interested persons are requested to send comments regarding the information collection by August 14, 1998 to the Office of Information and Regulatory Affairs, OMB (address above).

VI. Comments

Interested persons may by September 28, 1998, submit to the Dockets Management Branch (address above) written comments regarding this proposed rule. Two copies of any comment are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

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, it is proposed that 21 CFR part 812 be 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, 356, 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 shall submit to FDA a supplemental application if the sponsor or an investigator proposes a change in the investigational plan and obtains FDA approval under § 812.30(a) of any such change, and IRB approval as applicable (see §§ 56.110 and 56.111 of this chapter), before implementation. If a sponsor intends to conduct an investigation that involves an exception to informed consent under § 50.24 of this chapter, a 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 days of making these changes.

(i) *Developmental changes.* 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) 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. The requirements in paragraph (a)(1) of this section regarding IRB approval for such changes are described in paragraph (a)(3)(iii)(B) of this section.

(iii) *Definition of credible information*—(A) Credible information to support developmental changes in the device (including manufacturing changes) is defined as the information generated from the design control procedures under § 820.30.

(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 evidence of IRB chairperson (or designee) approval, in accordance with the expedited review procedures described in § 56.110 of this chapter, the concurrence or recommendation of a data safety monitoring board, or peer reviewed published literature supporting the change, as appropriate.

(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-calendar 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 a statement that no new risks were identified by appropriate risk analysis and that the verification and validation testing demonstrated that the design outputs met the design input requirements.

(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; for changes related to the rights, safety or welfare of the subjects, a letter of approval from the IRB chairperson (or designee). For changes related to the scientific soundness of the investigational plan or validity of the data, documentation of the concurrence/recommendation of the data safety monitoring board, or peer reviewed published literature supporting the change, as appropriate.

(v) *Review of the Notices.* If, at any time during the course of the investigation, FDA has reason to believe that the change(s) made in accordance with paragraphs (a)(3)(i) or (a)(3)(ii) of this section did not meet the applicable criteria, the agency will notify the sponsor that the change(s) required approval under paragraph (a)(1) of this section before being implemented. Upon receipt of such notification, the sponsor shall either suspend the investigation or revert to an investigation of the unmodified device or protocol until the change is approved under paragraph (a)(1) of this section.

(4) *Changes submitted in annual report.* The requirements of paragraph (a)(1) of this section do not apply to minor changes to the investigational plan that do not involve developmental, manufacturing, or protocol changes (i.e., 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: June 16, 1998.

William B. Schultz,

Deputy Commissioner for Policy.

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