DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 20 and 814

[Docket No. 91N–0404]

RIN 0910–AA09

Medical Devices; Humanitarian Use Devices

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is issuing a final rule to implement the provisions of the Safe Medical Devices Act of 1990 (the SMDA) regarding humanitarian use devices (HUD's). A HUD is a device that is intended to benefit patients by treating or diagnosing a disease or condition that affects or is manifested in fewer than 4,000 individuals in the United States per year. This final rule prescribes the procedures for submitting humanitarian device exemption (HDE) applications, amendments, and supplements; procedures for obtaining an extension of the exemption; and the criteria for FDA review and approval of HDE's. The purpose of this HDE is, to the extent consistent with the protection of the public health and safety and with ethical standards, to encourage the discovery and use of devices intended to benefit patients in the treatment or diagnosis of diseases or conditions that affect fewer than 4,000 individuals in the United States.

DATES: This final rule is effective October 24, 1996.

Written comments on the information collection requirements should be submitted by August 26, 1996.

ADDRESSES: Submit written comments on the information collection requirements to the Dockets Management Branch (HFA–305), Food and Drug Administration, 12420 Parklawn Dr., rm. 1–23, Rockville, MD 20857. All comments should be identified with the docket number found in brackets in the heading of this document.

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

SUPPLEMENTARY INFORMATION:

I. Background

On November 28, 1990, the President signed into law the SMDA (Pub. L. 101–629). In enacting the SMDA, Congress sought to improve the Medical Device Amendments of 1976 (the amendments). The amendments were the first legislative effort to establish a comprehensive framework to regulate medical devices and to ensure their safety and effectiveness. Congress subsequently recognized that for diseases and conditions affecting small populations, a device manufacturer's research and development costs could exceed its market returns, thereby creating an impediment to the development of such devices. In the SMDA, Congress enacted an amendment to section 520(m) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 360j(m)) to create an incentive for the development of devices for use in the treatment or diagnosis of diseases or conditions affecting a small number of individuals.

Accordingly, section 520(m) of the act authorizes FDA, by regulation, to exempt a HUD from the effectiveness requirements of sections 514 and 515 of the act (21 U.S.C. 360d and 360e) (i.e., ''reasonable assurance that the device is effective'') provided that: (1) The device is to be used to treat or diagnose a disease or condition that affects fewer than 4,000 individuals in the United States; (2) the device would not be available to a person with such a disease or condition unless the exemption is granted; (3) no comparable device (other than a device that has been granted such an exemption) is available to treat or diagnose the disease or condition; and (4) the device will not expose patients to an unreasonable or significant risk of illness or injury, and the probable benefit to health from using the device outweighs the risk of injury or illness from its use, taking into account the probable risks and benefits of currently available devices or alternative forms of treatment.

As specified in the statute, an HDE is valid for a term of 18 months from the date of approval but can be extended at 18-month intervals as long as certain approval criteria are met. Under section 520(m)(5) of the act, an exemption may only be initially granted in the 5-year period commencing on the effective date of this rule, although extensions may continue to be granted after the expiration of the initial 5-year period. Section 520(m) of the act also states that a HUD cannot be sold for an amount that exceeds the costs of research and development, fabrication, and distribution. In addition, such devices may only be used in facilities that have established a local institutional review board (IRB) to supervise clinical testing of devices, and after an IRB has approved the use of the device to treat or diagnose the specific rare disease (section 520(m)(3) and (m)(4) of the act).

On December 21, 1992 (57 FR 60491), FDA published a proposed rule on humanitarian use devices in the Federal Register. The proposed rule would have amended the investigational device exemption (IDE) regulations at part 812 (21 CFR part 812). At that time, FDA believed that amending the IDE regulations would be preferable to creating a new part to its premarket approval regulations because part 812 already contains provisions on IRB review and approval, patient informed consent, and limitations on charging. In the proposed rule, FDA explicitly invited comment on ''the advantages or disadvantages of using the IDE regulation as the means to implement section 520(m) of the act, as well as the desirability of using other alternative methods of implementation'' (57 FR 60491 at 60492).

FDA received 11 comments on the proposed rule. In general, most of the comments opposed including the HDE provisions in part 812. These comments asserted that applying the IDE regulations would make the HDE process more burdensome, discourage HUD development, prevent firms from promoting a HUD or distributing information about a HUD, preclude firms from obtaining third party reimbursement for a HUD, and increase a firm's liability insurance costs. In addition, these comments asserted that this approach would be contrary to the intent behind section 520(m) of the act which, some comments claimed, was to facilitate marketing of HUD's rather than clinical investigations involving HUD's. Three comments suggested that FDA implement section 520(m) of the act by creating special marketing procedures for HUD's under the premarket approval regulations of part 814 (21 CFR part 814), which implement section 515 of the act. One of these comments stated that FDA should issue a new proposal requesting comments on this approach.

Upon further consideration, the agency agrees that placing the HDE provisions in the IDE regulations is inappropriate because section 520(m) of the act is intended to facilitate the discovery and use of HUD's rather than to promote their use in clinical studies. Accordingly, the agency has chosen to create a new subpart H under part 814, specifically addressing HUD's, thereby establishing these devices as legally marketed products under the act.

However, section 520(m) of the act, which provides for an exemption from the effectiveness requirements of sections 514 and 515, also establishes a number of specific requirements for HUD's that do not apply to medical devices that are reviewed for both safety and effectiveness. Therefore, while subpart H references many of the procedures and requirements set forth elsewhere in part 814, it also explicitly incorporates the statutory requirements of section 520(m) of the act.

The final rule is responsive to the comments FDA received on the proposed rule, which generally objected to the use of the IDE regulations and supported a marketing approval procedure for HUD's. As noted above, several comments specifically requested FDA to regulate HUD's by amending part 814 for device premarket approval applications. In accordance with the statute and the comments received, the general approach of this final rule is to treat HDE's as premarket approval applications (PMA's) that do not require evidence or review of effectiveness. FDA has followed the statutory provisions of section 520(m) of the act closely in issuing this final rule, and the differences between the PMA and HDE approval process reflect the requirements established by Congress for an HDE.

The agency has determined that a reproposal is neither necessary for reasoned decisionmaking nor desirable as a matter of policy. As noted above, the proposed rule invited comments on alternative approaches, including the one now adopted. The comments FDA received contained significant and thoughtful analysis in favor of the approach being adopted in this final rule. Accordingly, the agency has concluded that there is no legal requirement to repropose. Moreover, the SMDA provided that FDA should issue regulations implementing section 520(m) of the act within 1 year of the statute's enactment. Further delay caused by reproposal, therefore, would be inconsistent with the legislative intent of section 520(m) of the act.

II. Summary of the Final Rule

A HUD is approved for marketing through an HDE application filed in accordance with the requirements of this final rule. An HDE application is a PMA application that is not required to contain clinical data demonstrating ''effectiveness'' (defined under § 860.7(e)(1) (21 CFR 860.(e)(1))) as ''reasonable assurance * * * based upon valid scientific evidence, that in a significant portion of the target population, the use of the device for its intended uses and conditions of use, when accompanied by adequate directions for use and warnings against unsafe use, will provide clinically significant results''). An HDE application will contain all other information ordinarily required in a PMA. In addition, an HDE application will require certain special information to satisfy the statutory requirements established by section 520(m) of the act.

A. HUD Designation

Under Subpart H, marketing approval for a HUD is accomplished in two distinct steps. First, the sponsor of a HUD must submit a request to FDA's Office of Orphan Products Development (OOPD) seeking a determination that the disease or condition which the device is intended to treat or diagnose affects or is manifested in fewer than 4,000 individuals in the United States per year. FDA added the qualifying phrase ''per year'' in order to clarify this provision of the statute. The agency believes that defining the criteria on a per year basis is consistent with the intent of section 520(m) of the act (i.e., to provide an incentive for the development of devices to be used in the treatment or diagnosis of diseases or conditions affecting small patient populations), whereas a point prevalence definition would be considerably more restrictive and provide less of an incentive for the development of such devices. In response to comments, FDA also has added ''or is manifested'' to the definition of a HUD in order to establish that HUD designation may be appropriate in cases where more than 4,000 people have the disease but fewer than 4,000 manifest the condition.

A request for HUD designation may be made at any time, and FDA encourages applicants to submit the request at the earliest possible time. In the request for designation, the applicant should include information that addresses the following three areas. First, the proposed indication(s) for use should be precisely defined within the context of current medical and scientific knowledge. If the proposed indication represents a subset of a larger, more common disease or condition, the applicant should provide a justification for limiting the patient population to this subset. Factors such as identification of the basic pathologic process, chronic versus acute nature of the disease or condition, age of the patient, compliance history, or mental competence may also create a viable subset, but the applicant is responsible for demonstrating that the defined population is medically plausible. Some devices may be used to achieve similar functions across a broad spectrum of diagnoses. For example, some apheresis devices are approved for separation of blood components, generally, and not approved on a disease by disease basis. In this situation, the appropriate prevalence would be determined by the combined use of the device for all diagnostic indications.

Second, in order to permit an understanding of the use of the device for the proposed indication, the request for HUD designation should also include a brief description of the device, including illustrations, as well as a discussion of its principle of operation.

Finally, in order to demonstrate that the rare disease or condition affects or is manifested in fewer than 4,000 people in the United States per year, the request should include documentation, with appended authoritative references, estimating the target population. For diagnostic devices, the documentation should demonstrate that fewer than 4,000 patients in the United States per year would be subjected to diagnosis with the device. FDA recognizes that, in some cases, the number of patient contacts with a device may exceed one per patient. Such devices may still qualify for HUD designation as long as the total number of patients treated or diagnosed with the device is less than 4,000 per year in the United States.

Within 45 days of receiving a request for HUD designation, OOPD will issue its determination based upon the information submitted by the sponsor as well as OOPD's own research and consultation. In some cases, OOPD may consult with the Center for Devices and Radiological Health (CDRH) regarding the proposed patient population to be treated or diagnosed with the device. In response to the designation request, OOPD will either approve the request, return it pending submission of additional information, or disapprove the request. If the request for designation does not contain all of the information required under § 814.102(a), it will be returned to the applicant with a description of the deficiencies. If the applicant chooses to address the deficiencies and resubmit the request for HUD designation, OOPD will reevaluate the application. The request for HUD designation may be disapproved if: (1) There is insufficient evidence to support the estimate that the disease or condition which the device is designed to treat or diagnose affects or is manifested in fewer than 4,000 people in the United States per year; (2) FDA determines that, for a diagnostic device, 4,000 or more patients in the United States would be

subjected to diagnosis using the device per year; or (3) FDA determines that the patient population defined in the request is not a medically plausible subset of a larger population. If FDA disapproves the request for HUD designation, the applicant may address the reasons for disapproval and resubmit the request.

B. HDE Application

If OOPD determines that a device is eligible for designation as a HUD, this determination must be included or referenced in the HDE application that is subsequently submitted to the Office of Device Evaluation (ODE), CDRH, FDA. The agency believes that this two-step process will make optimal use of its own time and resources as well as that of HDE applicants by ensuring that HDE's are only prepared and reviewed for devices genuinely eligible for HUD status.

The HDE application, which should be submitted to ODE, is similar in both form and content to a PMA application submitted under § 814.20. For example, the HDE application must contain a summary of the indications for use of the device, significant physical and performance characteristics of the device, and any clinical and nonclinical data that are relevant to evaluating the safety and probable benefit of the device. The application must contain sufficient information for FDA to determine, as required by the statute, that the device does not pose an unreasonable risk of illness or injury to patients and that the probable benefit outweighs the risk of injury or illness from its use, taking into account the probable risks and benefits of currently available devices or alternative forms of treatment. FDA believes that such a determination cannot be made in the absence of most of the information required to be filed under a full PMA submitted in accordance with § 814.20.

However, the HDE is not required to contain the results of scientifically valid clinical investigations demonstrating that the device is effective for its intended purpose. While in some instances there may be little or no clinical experience with the device, an applicant is required to include such information in the HDE whenever it is available. Depending upon the nature of the device and its associated risks, FDA may require that clinical data regarding the safety of the device be collected in support of an HDE. Clinical investigations of a HUD are subject to the requirements of part 812, which may require the submission of an IDE to FDA if the device study poses a ''significant risk'' (§ 812.3(m)).

An HDE application must also contain information that will allow FDA to make the other determinations required by section 520(m) of the act. Specifically, the HDE must contain information to enable FDA to determine that: (1) The device would not otherwise be available unless an HDE were granted, and (2) no comparable device (other than another HUD approved under this subpart or a device being studied under an approved IDE) is available to treat or diagnose the disease or condition. In order to address why the device would not otherwise be available unless an exemption is granted, the applicant should estimate the number of patients who would be required to generate data to support a full PMA and explain why such a study is not feasible or why the cost of conducting such a study could not reasonably be expected to be recovered. (See S. Rept. 513, 101st Cong., 2d sess. 41 (1990).)

C. Charging for the Device

Section 520(m) of the act does not permit devices marketed under the HDE provision to be sold for a price that exceeds the costs of research and development, fabrication, and distribution of the device. Therefore, the final rule requires that an HDE application include a report by an independent certified public accountant verifying that the amount to be charged does not exceed the costs of research and development, fabrication, and distribution for the device. FDA also expects research and development costs to be treated (i.e., capitalized or expensed) in accordance with guidelines or requirements of the Financial Accounting Standards Board.

D. FDA Action

As with a PMA application, FDA will notify the submitter of an original HDE or an HDE supplement, within 45 days, whether the submission is sufficiently complete to permit substantive review. FDA may refuse to file an HDE or HDE supplement if: (1) The application is incomplete; (2) FDA determines that there is a comparable device available, other than under this exemption or an approved IDE, to treat or diagnose the disease or condition for which approval of the HUD is being sought; or (3) the application contains a false statement of material fact.

If the HDE is filed, the agency will act upon the application within 180 days from the time such application is received by the agency. FDA believes that this timeframe will generally be required to perform a thorough evaluation of a HUD's safety, probable benefit, proposed labeling, and any appropriate conditions of approval. If the HDE applicant believes that the HUD may meet the agency's criteria for expedited review (i.e., the device is for a life-threatening or irreversibly debilitating condition, provides a clear, clinically meaningful advantage over existing technology, or meets a specific public health need, as determined by FDA), the applicant is encouraged to raise this issue when submitting the application. In reviewing an HDE, the same options available to FDA under the PMA regulations (namely, issuing an approval order, an approvable letter, a not approvable letter, or a denial of approval order) are available, although the criteria for each action are different in some important respects from §§ 814.44 and 814.45 of the PMA regulations. For example, as specified by the statute, one of the criteria for approval of an HDE is that the device would not otherwise be available unless this exemption were granted. Therefore, if an HDE applicant has established that the affected patient population is fewer than 4,000 per year but each patient may require numerous devices, the agency may determine that the device would be commercially viable and thus not meet this statutory requirement for the exemption. (See H. Conf. Rept. 959, 101st Cong., 2d sess. 28 (1990).)

Approval of an HDE is valid for a period of 18 months. After that time, the device may continue to be marketed only if the HDE holder has sought and obtained an extension of the exemption as provided for in § 814.120. During the period of marketing approval, HDE holders are strongly encouraged to collect data that may later be submitted in support of a full PMA.

E. Labeling for a HUD

Because labeling for a humanitarian use device is not addressed in section 520(m) of the act, the labeling requirements for a HUD reflect the comments received on this issue and the agency's desire to disclose pertinent information regarding HUD's to health care practitioners. Therefore, under the final rule, the labeling for a HUD will state that the device is a humanitarian device, that use of the device to treat or diagnose a specific disease or condition is authorized by Federal law, and that the effectiveness of the device for the specific use has not yet been demonstrated.

F. Postapproval Requirements

During the period of marketing approval, the HDE holder is subject to the requirements of the good manufacturing practice (GMP)

regulations unless an exemption is sought by the applicant and granted by FDA. Devices approved under subpart H are also subject to the postapproval requirements and reports set forth under subpart E of part 814, including medical device reporting requirements (part 803 (21 CFR part 803)) and labeling requirements (21 CFR parts 801 and 809). In addition, a holder of an approved HDE is required to notify FDA of the withdrawal of approval for the use of a HUD by a reviewing IRB within 5 working days after being notified of the action.

G. Extension Requests

As stated previously, approval of an HDE differs in several important respects from the approval of a PMA submitted under § 814.20. By statute, approval of an HDE is valid for a period of 18 months, after which the device may no longer be marketed unless the HDE holder has sought and obtained an extension as provided for in § 814.120 of subpart H. The request must be submitted prior to expiration of marketing approval. FDA will review extension requests within 90 days; therefore, in order to avoid the risk of a lapse in approval, the request must be submitted at least 90 days prior to the expiration. The request for extension shall be clearly marked as such, and should be submitted to ODE.

The request should also include an update of the information that was originally submitted in the HDE application, as well as a separately bound volume which addresses the device's continuing qualification for HUD designation. (ODE will submit this volume to OOPD for review.) The request should include an update of the information originally required (§ 814.104(c)(2), (c)(3), and (c)(5)) as well as information describing the applicant's experience with the device since the HDE was initially approved (§ 814.120(b)(4)). This shall include any new safety information that is known or reasonably should be known to the applicant, medical device reports made pursuant to part 803, any data generated from postmarketing studies, and any published or unpublished information that is known or reasonably should be known that may affect an evaluation of the safety of the device or that may affect the statement of contraindications, warnings, precautions, and adverse reactions in the labeling. In order to allow the applicant adequate time to prepare the request for extension, FDA would expect the request for extension to include the applicant's experience with the device based on the first 12-month period following the most recent approval of the HDE. The request shall also include a summary of any changes to the device (as permitted under § 814.108 of the final rule).

The HDE holder must also include data demonstrating that the number of devices shipped or sold is consistent with the earlier determination by OOPD that the device is for a disease or condition affecting or manifested in fewer than 4,000 patients per year. If the number of devices shipped or sold during the previous 12 months of marketing approval exceeds 4,000, the HDE holder should include an explanation and estimate of the number of devices used per patient. If a single device is used on multiple patients, the applicant shall submit an estimate of the number of patients treated or diagnosed using the device together with an explanation of the basis for the estimate. If experience during the period of marketing approval so indicates, the agency may determine that the device no longer meets the statutory requirements for HDE's.

Under the final rule, FDA will respond to extension requests within 90 days of receipt of such a request, or the request shall be deemed approved. Requests for extension may be granted more than once and may be granted even after the expiration of the initial 5-year period. In the event that the HDE holder does not wish to extend the HDE, a final report is required to be submitted no later than 90 days following the expiration of the period of marketing approval (§ 814.126(b)(i)).

H. IRB Approval

Section 520(m)(4) of the act states that a HUD may only be used in facilities that have established, in accordance with FDA regulations, ''a local institutional review committee [commonly known as an institutional review board or IRB] to supervise clinical testing of devices in the facilities.'' The statute also requires an IRB to approve the use of the HUD before the device is administered to humans. In accordance with this statutory requirement, FDA has specified in subpart H of part 814 that the HDE holder must ensure that the HUD is administered only to patients at health care facilities having an IRB.

IRB's which oversee the use of a HUD should be constituted and act in accordance with the agency's regulations governing IRB's (21 CFR part 56), including responsibility for continuing review of use of the device. FDA has codified this requirement in § 814.124. The agency does not believe the statute intends to require IRB review and approval for each individual use of the HUD. FDA has interpreted the statute to permit the IRB to approve the use of the device in general, use of the device for groups of patients meeting certain criteria, or use of the device under a treatment protocol. If it so wishes, an IRB may specify limitations on the use of the device based upon one or more measures of disease progression, prior use and failure of any alternative treatment modalities, reporting requirements to the IRB or IRB chair, appropriate followup precautions and evaluations, or any other criteria it determines to be appropriate.

It should be emphasized that under the final rule (§ 814.124), it is the HDE holder who is responsible for ensuring that the HUD is not administered to or implanted in a patient prior to obtaining IRB approval at the health care facility. An HDE holder may wish to enforce this requirement by not shipping the HUD to the health care facility until it has received confirmation of IRB approval. In order to provide flexibility to the approval requirement, FDA has included a provision that permits an IRB located at a treatment facility to defer (in writing) to another similarly constituted IRB that has agreed to assume responsibility for initial and continuing review of the use of the device.

I. Informed Consent

Section 520(m) of the act does not require that informed consent be obtained before a HUD is used. Therefore, subpart H of the final rule does not include a provision requiring compliance with the informed consent regulations (part 50 (21 CFR part 50)). FDA has decided that a humanitarian device exemption, which provides for temporary marketing approval, does not constitute ''research'' or an ''investigation,'' which would normally require informed consent. A HUD is intended to benefit patients who have a rare disease or condition rather than to generate data to support a finding of effectiveness. FDA believes, therefore, that waiving compliance with the informed consent regulations is consistent with section 520(m) of the act because the statute expressly uses the phrase ''to the extent consistent with the protection of the public health and safety and with ethical standards'' rather than requiring informed consent from each patient. Notwithstanding the above, FDA does not intend to preempt any applicable requirement for informed consent that may be imposed as a matter of State law or institutional policy.

As a point of clarification, however, if a HUD is the subject of a clinical

investigation, informed consent from the patients involved in the study would be required. Thus, if a holder of an approved HDE wishes to collect safety and effectiveness data in support of a PMA, compliance with part 50 would be required at those institutions participating in the investigation.

III. Response to Comments

The proposed rule consisted of 10 provisions. Nine provisions proposed amending the existing IDE regulations to establish content requirements for HDE applications and supplements, as well as FDA action on such applications; the tenth provision proposed a certification statement for HDE applications. FDA received 11 comments on the proposed rule. As discussed earlier, most of the comments generally disagreed with the proposed amendments to the IDE regulations or sought changes to the proposed HDE provisions. One comment supported the proposed rule without any changes. A summary of the comments and the agency's response to them is provided below.

A. General Comments

1. Several comments asserted that the proposed rule would require too much data and information from HUD sponsors.

FDA disagrees with these comments. In granting an HDE, the agency must have sufficient information to enable it to make the determinations required by section 520(m) of the act, including the pivotal determinations that the device will not expose patients to an unreasonable or significant risk of illness or injury and that the probable benefit to health from use of the device outweighs the risk of injury or illness, taking into account the probable risks and benefits of currently available devices or alternative forms of treatment. The agency can only make these determinations if the sponsor provides FDA with sufficient data, including information about device design, materials, laboratory and animal studies, as well as any available clinical experience with the device.

2. One comment claimed that the proposal had little value because long PMA review times would mean that few HUD's could be approved for use before section 520(m) of the act expired (since the HDE authority expires 5 years from the date this final rule takes effect).

FDA disagrees with this comment. Average FDA review times for original PMA's have been decreasing. In addition, there is not necessarily a correlation between PMA review times and review times for HDE's. FDA believes that it will be able to meet the 180-day review time set forth in subpart H. Moreover, although an HDE is initially approved for only 18 months, extensions of the exemption period may continue to be granted after the end of the 5-year period.

3. One comment recommended amending the PMA regulations instead of the IDE regulations and also relieving HUD's from certain IDE requirements. The comment would amend § 812.2(b) so that a HUD would be considered to have an approved IDE and be subject only to the ''abbreviated requirements'' of the IDE regulations.

As recommended in the comment, FDA has chosen to amend the PMA regulations rather than the IDE regulations as a means of implementing section 520(m) of the act. The agency declines, however, to adopt the recommended change to § 812.2(b). Section 812.2(b) states, in essence, that an investigation involving a nonsignificant risk device shall be considered as having an approved IDE as long as certain regulatory requirements are met. Although section 520(m) of the act only permits approval of HDE's if the device ''will not expose patients to an unreasonable or significant risk,'' it is possible that a HUD could be tested in an investigation involving procedures that present a serious risk to a subject's health or safety (i.e., a ''significant risk'' study that requires an FDA-approved IDE). Furthermore, rare diseases for which HUD's are developed may be serious conditions requiring an intervention that poses some risk of harm. Consequently, it would be inappropriate to presume, or to infer that Congress intended, that all HUD's qualify as ''nonsignificant risk'' devices, as proposed in the comment.

4. The same comment, as part of its recommendation to place the HUD requirements in part 814, suggested conforming changes to the ''Purpose'' and ''Definitions'' sections at §§ 814.2 and 814.3, respectively, to account for HUD's. The comment would create a new subpart F in part 814, entitled ''Humanitarian Device Applications,'' that would contain a general statement on HUD's, prescribe labeling requirements (including a required statement showing that the device is a humanitarian device whose use is limited to a specific treatment or diagnosis of a disease or condition and has not been shown to be effective), and prohibit commercialization (although it would permit ''incidental'' profits which exceed ''good faith estimates of costs''). The comment patterned its suggested HDE application requirements after the PMA application requirements in § 814.20, recommending that an HDE application include, among other things, information on the device's indications for use, a description of the device (including an explanation of how the device functions, the basic scientific concepts forming the basis for the device, and the device's significant physical and performance characteristics), a description of the device's marketing history in the United States and in foreign countries, a summary of safety studies or other information, and conclusions drawn from safety studies or other information. The comment further suggested that the application contain a complete description of the device, its functional components or ingredients, the device's properties relevant to the diagnosis, treatment, prevention, cure, or mitigation of a disease or condition, its operating principles, a discussion of current good manufacturing practices applied to the device, references to any performance standard under section 514 of the act or the Radiation Control for Health and Safety Act of 1968 or any voluntary standard relevant to any aspect of the device's safety ''that is known to or that should reasonably be known to the applicant,'' including information demonstrating how the device meets or deviates from a performance standard or deviates from a voluntary standard.

The comment further suggested that FDA create a new provision on labels and that the labels provide the manufacturer, packager, or distributor's name and place of business, the quantity of contents (if appropriate), and a ''Caution'' statement declaring:

> CAUTION—Humanitarian Device. Limited by Federal (or United States) law to use in the treatment or diagnosis of [specify disease or condition]. The effectiveness of this device in treating or diagnosing [specify disease or condition] had not been demonstrated.

The label would also describe ''all relevant contraindications, hazards, adverse effects, interfering substances or devices, warnings, and precautions'' and not represent that the device is effective for the humanitarian use.

Additionally, the comment would have the application contain information showing why any amount to be charged does not constitute commercialization of the device, an environmental assessment or request for categorical exclusion under part 25, and ''such other information as FDA may request.'' The comment would also authorize FDA to refer to information in a master file or to other information submitted to FDA by a person other than the applicant, but only if the applicant had written authorization to

refer to such information. The comment would have FDA return a master file to the person who filed it if no one referenced that master file within 5 years after it was submitted to FDA.

The agency agrees, in part, with the comment and has revised the final rule to amend the PMA regulations by adding a new subpart concerning premarket approval for HUD's. The agency elected to adopt this approach because it was persuaded by the comments that section 520(m) of the act was intended to encourage marketing rather than investigational use of humanitarian use devices. While it exempts a HUD from demonstrating effectiveness, section 520(m) of the act establishes some requirements for approval of HUD's that are similar to the IDE requirements under section 520(g). For example, section 520(m) of the act states that the HUD provisions should function to the extent ''consistent with the protection of the public health and safety and with ethical standards'' and require IRB approval before the use of the device.

Thus, FDA used the PMA provisions suggested by the comments as a template for the format and content of an HDE and issued different or additional provisions when such changes were required by the statute. Accordingly, § 814.104(c)(4) requires the application to contain most of the information required under § 814.20(b), with the exception of clinical data demonstrating the effectiveness of the device. In lieu of such evidence, the HDE must nevertheless contain ''summaries, conclusions, and results of all clinical experience or investigations (whether adverse or supportive) reasonably obtainable by the applicant which are relevant to an assessment of the risks and probable benefits of the device.'' FDA emphasizes that data or information, whether derived from clinical or nonclinical studies or laboratory experience, relating to the device's use in humans may be critical in determining whether the risk of illness or injury outweighs the probable benefit from using the device, taking into account the probable risks and benefits of currently available devices or alternative forms of treatment. While an HDE applicant will not be required to generate data from clinical investigations to demonstrate the device's effectiveness, clinical data may sometimes be necessary in order to demonstrate this risk/benefit relationship.

FDA agrees, in part, with the comment's suggested format and content for the labeling of a HUD. FDA believes that the label should disclose that the effectiveness of the device has not yet been demonstrated. The agency does not, however, believe that the HUD label needs to contain the word ''Caution,'' because that term may imply that the device exposes the patient to dangers not ordinarily associated with lawfully marketed products. Also, in view of the safety analysis that FDA will perform in reviewing HDE's, as well as the requirement of IRB approval, the agency does not believe that the word ''Caution'' is necessary.

In response to the comment suggesting that FDA return a master file to the person who submitted it in the event that the file is not referenced within 5 years after its submission to FDA, the agency notes that such a requirement already exists in part 814 (§ 814.20(c)) and that it is therefore applicable to applications submitted under subpart H.

5. As part of its recommendation to amend the PMA regulations to include HDE's, one comment would create a new reporting provision to require applicants to update safety information ''that may reasonably affect the evaluation of the safety of the device or that may reasonably affect the statement of contraindications, warnings, precautions, and adverse reactions'' in the labeling. The comment would require compliance with the medical device reporting requirements in part 803 and would require the submission of reports at 6-month intervals after approval of the HDE application. These reports would identify changes affecting the device and contain a summary and bibliography of unpublished reports involving the device or related devices that are known to or should reasonably be known by the applicant as well as reports in the scientific literature. The comment would not require the applicant to provide copies of reports in the scientific literature unless FDA notified the applicant that it should submit those reports. The comment's suggested provision would be similar to the existing reporting requirements for PMA's at § 814.84.

The agency agrees, in part, with the comment. Under § 814.126, an HDE approved under subpart H is subject to the postapproval requirements and reports as required for PMA's (subpart E of part 814). In addition, HDE holders must provide the IRB of record with a copy of any report submitted in compliance with the requirements of part 803. Also, under § 814.126(b)(1), if a request for extension of the exemption is not submitted, a final report must be submitted to the agency no later than 90 days after the expiration of the marketing approval. This final report should contain an estimate of the number of devices shipped or sold and the number of patients treated or diagnosed, information regarding the retrieval or disabling of unused devices, a summary of results or conclusions with regard to the clinical use of the device, and a summary of the medical device reports submitted under part 803. The final report should also contain a summary and bibliography of published and unpublished data, reports, and studies involving the device that are known to or should reasonably be known by the applicant and were not previously submitted to the agency.

In addition to the above reports, § 814.124(b) requires the holder of an approved HDE to notify FDA within 5 working days of any withdrawal of approval for use of a HUD by a reviewing IRB. Finally, § 814.126(b)(2) instructs applicants to maintain records of the names and addresses of the facilities to which the HUD's have been shipped, correspondence with reviewing IRB's, and any other information requested by a reviewing IRB or FDA. All such records should be maintained for the duration of the period that a HUD is approved for marketing.

The agency declined to accept the comment's suggestion for the submission of periodic reports (at 6-month intervals) because FDA believes it is unlikely that many changes or significant new information ordinarily would be generated for a HUD in such a short period of time.

6. As part of its suggestion that FDA amend the PMA regulations rather than the IDE regulations, one comment proposed a new provision describing where an HDE application should be sent.

The agency agrees that such a provision is necessary and has specified in § 814.104(e) that HDE applications, amendments, supplements, requests for extension, and related correspondence (excluding reports submitted under part 803) should be sent or delivered to the Document Mail Center (HFZ–401), Office of Device Evaluation, Center for Devices and Radiological Health, Food and Drug Administration, 9200 Corporate Blvd., Rockville, MD 20850.

B. Specific Provisions and Comments

Proposed § 812.1(b) Scope

7. Proposed § 812.1(b) would have added HDE provisions to the IDE regulations. Because the agency has elected to create a new subpart H under part 814, the agency has renumbered this provision as § 814.100 and

redesignated it as ''Purpose and Scope.'' Under this section, FDA has also modified the reference to uses other than humanitarian uses. The proposed rule stated that the HDE provisions applied only to humanitarian uses; FDA has modified this statement to note that persons seeking approval of non-HUD uses must comply with the premarket approval or premarket notification provisions of the regulations, as appropriate.

Proposed § 812.3(d) Humanitarian Use Device (HUD)

8. Proposed § 812.3(d) defined a HUD as ''a device that is intended for use in the treatment or diagnosis of a disease or condition that affects fewer than 4,000 individuals in the United States and that otherwise meets the requirements in 21 U.S.C. 360j(m)(2).''

Three comments recommended revising the definition of a HUD. The comments would revise the definition to include manifestations of a disease so that, even if the total number of patients who had a disease or condition exceeded 4,000, one could obtain an HDE if the patient population that manifested the disease was less than 4,000.

FDA agrees with the comments and has modified the definition of a HUD to state that the device must be intended for use in the treatment or diagnosis of a disease or condition that ''affects or is manifested in fewer than 4,000 individuals in the United States per year.'' This definition has been added to the existing definition section of part 814. The agency has also modified the definition to clarify that the number of affected patients is determined at the time the request for HUD designation is submitted under § 814.102, and again each time a request for extension is submitted under § 814.120. Regarding this prevalence determination, FDA would not withdraw approval of an HDE solely because it is subsequently determined that the disease or condition for which the HUD is intended affects or is manifested in more than 4,000 people in the United States per year. However, this fact may serve as a basis for disapproving an extension request.

9. One comment suggested revising the definition of a HUD by paraphrasing section 520(m)(2)(A) through (m)(2)(C) of the act.

FDA declines to amend the definition as suggested by the comment. The final rule's definition of a HUD incorporates language from section 520(m)(2)(A) of the act and conveys that, based solely on the estimated prevalence or manifestation of a rare disease or condition, a particular device has been found eligible for review under subpart H. This eligibility will be determined by the division within OOPD with the most expertise in these matters. The statutory provisions which the comment suggests for inclusion in the definition of a HUD are requirements for approval of the HDE application (i.e., the device would not otherwise be available, there is no comparable device, the device would not expose patients to an unreasonable or significant risk of illness or injury, and the benefits of using the device outweigh the risks). Review of the HDE application and these approval decisions will be made by ODE, which is the group within CDRH that reviews PMA's. Furthermore, FDA believes that it is useful to have a term that describes those devices that are eligible for an HDE, i.e., qualify as a humanitarian use device, but have not yet been granted marketing approval under subpart H.

10. One comment suggested defining ''HDA'' as ''any humanitarian device application, including all information submitted with or incorporated by reference therein.'' The comment also suggested defining ''safe'' or ''safety,'' for HUD purposes, as meaning that the device ''will not expose patients to an unreasonable or significant risk of illness or injury and the device's probable benefit outweighs the risk of injury or illness associated with its use.''

FDA declines to adopt this suggestion. Section 520(m) of the act is titled ''Humanitarian Device Exemption'' and authorizes the agency to grant an exemption from the effectiveness requirements of sections 514 and 515 of the act. Therefore, the agency will refer to an application submitted pursuant to section 520(m) of the act as a ''humanitarian device exemption application'' or ''HDE.'' This represents a more accurate description of the application itself.

Regarding the comment's suggested definition of ''safe'' or ''safety,'' FDA notes that this definition is similar to the statutory requirement that a HUD ''not expose patients to an unreasonable or significant risk of illness or injury, and the probable benefit to health from using the device outweighs the risk of injury or illness from its use, taking into account the probable risks and benefits of currently available devices or alternative forms of treatment.'' Because § 814.118 of the final rule includes failure to meet this criterion as a basis for denying or withdrawing approval of an HDE, FDA believes that repeating the risk-benefit concept in the definition section is unnecessary.

Proposed § 812.10 Waivers

FDA received four comments on the proposed waivers from the IDE requirements. Although the final rule does not waive any sections of the IDE regulations, the agency believes that some of the issues raised in the comments merit discussion or clarification.

11. One comment questioned whether clinical data generated under an HDE application would still qualify as ''valid scientific evidence'' under § 860.7. The comment asserted that, if clinical data generated under an HDE application is not ''valid scientific evidence'' within § 860.7, then there would be little incentive to submit an HDE application.

Although the final rule for HDE's provides for marketing approval under subpart H of part 814, rather than investigation under part 812, this comment does raise the issue of whether the HDE application, which is a marketing application under part 814, must contain ''valid scientific evidence'' as defined in § 860.7. FDA recognizes that there are a limited number of patients for whom a HUD may have been prescribed and that the device was likely to have been used in a treatment rather than research context. FDA, therefore, intends to exercise its discretion in applying § 860.7 to the data submitted in support of an original HDE or HDE extension request and not require the HDE to contain the same valid scientific evidence as other premarket approval applications. However, FDA urges HDE applicants, whenever possible, to try to ensure that clinical information submitted in support of an original HDE or an HDE extension request does constitute ''valid scientific evidence.''

12. One comment questioned the applicability of GMP regulations to HDE applicants, particularly where the applicant is a university or hospital.

The quality systems for FDA regulated products (food, drugs, biologics, and devices) are known as the good manufacturing practice regulations or GMP's. GMP requirements for devices (part 820 (21 CFR part 820)) were first authorized by section 520(f) of the act which was among the authorities added to the act by the 1976 Amendments (Pub. L. 94–295). GMP's are intended to ensure that the methods, facilities, and controls used for manufacturing, packing, storing, and installing a finished device are appropriate and will ensure that the device is safe for use.

The SMDA amended section 520(f) of the act, providing FDA with the explicit authority to add preproduction design validation controls to the GMP

regulation. FDA expects to publish a final rule revising the GMP regulations in the near future.

Under the final rule, HUD's will be subject to the GMP regulations, as are other legally marketed devices. The agency may require as a condition of approval that the HDE applicant demonstrate compliance with these regulations (e.g., through an inspection). However, consistent with the regulatory flexibility which FDA believes Congress intended in enacting the HUD exemption, the agency intends to focus primarily on those manufacturing practices that the agency deems most relevant to the safety of the device. An HDE applicant or holder who believes that he/she cannot comply or should not be held to GMP standards may request an exemption from such requirements (§ 820.1(d)). In evaluating such exemption requests, FDA will give overriding consideration to the risks posed by the device, the potential risks that a manufacturing defect might pose to patients, and the public health need for the device.

13. One comment suggested adding § 812.35(a) and (b) to the list of IDE requirements that would be waived for a HUD. Currently, § 812.35(a) requires a supplemental IDE if a sponsor or investigator proposes a change in the investigational plan that may affect the plan's scientific soundness or the subjects' rights, safety, or welfare. Section 812.35(b) requires sponsors to submit to FDA a certification of any IRB approval of an investigation or part of an investigation that is not included in an IDE. The comment asserted that these supplemental IDE requirements are time-consuming and deprive patients from receiving a device.

Because the agency has elected to create a new subpart H that provides for marketing approval for HUD's rather than amending the IDE regulations, the issue raised by the first part of this comment is moot. In reference to the suggestion that sponsors should not be required to submit supplemental applications to FDA when IRB approval is obtained, the agency agrees, and the final rule does not require FDA to be notified of such approval.

14. One comment asserted that the waivers in proposed § 812.10 would not adequately reduce the cost of preparing IDE's and PMA's.

Although proposed § 812.10 is not a part of the final rule, the agency notes that section 520(m) of the act is intended to encourage the discovery and use of devices intended to benefit patients in the treatment or diagnosis of diseases or conditions that affect small populations by granting an exemption from the effectiveness requirements of sections 514 and 515 of the act. Such an exemption from the effectiveness requirements should significantly lower the cost of preparing a marketing application.

Proposed § 812.20(e)(2) Information Required for HUD's

15. Proposed § 812.20(e)(2) would have required the agency to determine that the device would not be available to a person with a rare disease or condition without an exemption and that ''there is no comparable device, other than under this exemption, available to treat or diagnose such disease or condition.'' One comment would modify the reference to ''no comparable devices'' so that other investigational devices in addition to HDE-devices would not be considered as ''comparable devices.''

FDA agrees with the comment and has modified the provision, which is now codified at § 814.104(c)(2), to include devices under an approved IDE. FDA wishes to emphasize that a ''comparable'' device need not be identical to the device that is the subject of the HDE application in order for the agency to determine that the applicant's device does not qualify for the statutory exemption. In determining whether a ''comparable device'' exists, FDA will consider the device's intended use and technological characteristics and make a judgment regarding the degree to which it is similar to any lawfully distributed device (other than another HUD or a device under an approved IDE). The agency will use the information provided by the applicant as well as any other information at its disposal to determine whether a comparable device exists.

§ 812.27 Report of Prior Investigations

16. Although FDA did not propose any amendments to § 812.27, one comment suggested adding a new paragraph to § 812.27(a) to state:

> When long-term testing is required to justify the proposed investigation, the application must include: (i) A description of the long-term tests; (ii) a description of the test protocol and number of samples in the test; (iii) the rationale for the test and protocol; and (iv) a timetable for completing the tests.

Although the comment is no longer literally applicable because the final rule amends part 814 rather than part 812, the agency agrees in part with the comment. The HDE application, which is now part of the PMA regulations, must provide sufficient information about the device to permit the agency to determine that its use will not unduly put patients at risk and that there is some probable benefit to using the device. This determination requires the submission of preclinical testing, and in some cases clinical testing, to support such a finding. However, because section 520(m) of the act provides for initial humanitarian use exemptions only for 5 years from the effective date of the final rule, and because the term of an exemption or renewal is 18 months, the agency does not anticipate that many long-term tests will be performed in support of an original HDE application. When appropriate, FDA could provide for such testing as a condition of approval under § 814.116(c).

Proposed § 812.35(c) Request for Extension of a HUD Investigation

FDA received three comments pertaining to proposed § 812.35(c), which would have established certain requirements for requesting an extension of a HUD investigation.

17. One comment asserted that clinical investigations may prompt a sponsor to change a device's design or performance characteristics, but that submitting a supplemental application (to reflect the changes in the device) would be time consuming and would deny patients access to the modified device. The comment suggested adding a new provision stating that supplemental HDE applications are not required to be submitted to FDA if an IRB reviewed the device modification together with other relevant data and determined that the modification will not expose patients to additional risk. Additionally, the comment would require the sponsor to maintain a description of each device modification, a summary of all tests, a rationale for why the modification does not expose patients to additional risk, a modification to any long-term clinical investigation plans, and a copy of a letter from the IRB that reviewed the modification.

The agency declines to amend the rule as suggested by the comment. While section 520(m)(4)(B) of the act requires IRB approval for the use of a HUD, it is FDA that is required to determine the relative safety and potential benefit of the device for the intended patient population. Additionally, the agency notes that IRB's may not possess the technical or scientific expertise that may be required to review a supplemental application for device modifications. FDA regulations require IRB's to have members who ''shall be sufficiently qualified through the experience and expertise of its members * * * to promote respect for its advice and counsel in safeguarding the

rights and welfare of human subjects'' (21 CFR 56.107(a)). Thus, IRB members focus on ethical concerns rather than on the scientific and technological issues that supplemental applications usually address. Finally, the requirement for agency review of device modifications for HUD's is consistent with the procedures required for other types of marketing applications (PMA's and premarket notifications (510(k)'s)).

18. One comment addressed the preamble discussion for proposed § 812.35. The comment claimed that the preamble to the proposed rule erred in describing extensions of an HDE. The preamble to the proposed rule stated that, ''[a] request for an exemption extension which would allow the continuation of the investigation would have to contain any relevant new information as to the safety and effectiveness of the HUD or the prevalence of the disease or condition for which the exemption was first approved * * *'' (57 FR 60491 at 60493). The comment said that FDA should delete the word ''effectiveness'' because the HDE eliminates the need to comply with the effectiveness requirements in the act.

FDA agrees that an approved HDE relieves a party from the effectiveness requirements of sections 514 and 515 of the act. Accordingly, § 814.120 of the final rule, which provides for extensions of the exemption, does not require that effectiveness information be included with the request. The agency wishes to note, however, that clinical experience gathered under an HDE may provide information regarding a device's effectiveness that would be relevant to FDA's making the statutorily-mandated determination that ''the probable benefit to health * * * outweighs the risk of injury or illness * * *.'' In addition, § 814.118(a)(2) of the final rule states that a determination by FDA that the ''device is ineffective under the conditions of use prescribed, recommended, or suggested in the labeling thereof'' is sufficient grounds for denial of approval of an HDE or of a request for an extension. FDA believes that no device that is demonstrably ineffective can pass the ''probable benefit'' test. Therefore, while effectiveness data is not required for an extension of the exemption, if any such information is available, it should be submitted to aid the agency in making its benefit/risk determination. As the Conference Report states, ''this inquiry requires the Secretary to consider the efficacy and potential benefits of the device * * *'' (H. Conf. Rept. at 28).

19. One comment suggested a new provision on supplemental applications, specifying the types of supplements that would or would not require FDA approval. The changes suggested by the comment would mirror the requirements of the PMA regulations. The comment also suggested that supplements follow format and content requirements similar to those for original HDE applications (which, under the comment, would be similar to PMA requirements) and be subject to the same time periods for review as original HDE applications.

The agency agrees, in part, with the comment. Under the final rule (§§ 814.106 and 814.108), HDE amendments and supplements (with one exception) are subject to the same regulations and time periods as those for PMA's. The single exception under the final rule is that a request for a new indication for use of a HUD may not be submitted as a supplement, but instead shall be treated as a new application, requiring redesignation of HUD status and an original HDE (see § 814.110). As with PMA's, a major amendment to an original HDE or HDE supplement may extend the review period for 180 days, and failure to respond in writing to an agency request for an amendment within 180 days will result in the pending HDE or supplement being deemed voluntarily withdrawn by the applicant (see § 814.37).

20. One comment would amend the rule to add a new provision describing an applicant's obligations when requesting an extension of an HDE. Section 520(m)(5) of the act states that the agency may extend an exemption for an additional 18 months if the agency is able to make the same findings that were necessary to grant the initial request for an HDE exemption. The statute also requires applicants to supply information showing that the applicant is not selling the device for an amount that exceeds the cost of research and development, fabrication, and distribution. The comment would require applicants to provide such information, and require FDA to grant an extension if the request for an extension ''confirms the FDA's original findings'' and demonstrates compliance with the statutory prohibition against commercialization. The comment would also permit applicants to request, and FDA to approve, more than one extension.

The agency agrees with the comment. Section 814.120 of the final rule states that FDA may, in response to a request by the holder of an HDE, extend the HDE for an additional 18-month term. The contents of the extension request and the approval criteria parallel the statutory requirements and are set forth under § 814.120(b) and (c), respectively. The agency also agrees that extending an exemption more than once is consistent with section 520(m)(5) of the act.

Institutional Review Board Review

21. One comment would add a new provision describing an IRB's role, including requiring IRB's to presume that FDA approval of an HDE application establishes that a device is designed to treat or diagnose a disease or condition that affects fewer than 4,000 individuals in the United States. The comment would also confine the IRB's review to ''the patient's need for the device and the likelihood that the device is appropriate for the patient's condition or disease state.'' The comment would further state that an IRB may deny approval of the use of the device ''if it finds that the device has no potential to benefit the patient'' and require semiannual submissions to the holder of the approved HDE of ''all records of approvals for use of the humanitarian device.''

FDA agrees, in part, with the comment. Section 814.124(a) states that, before administering a humanitarian use device to humans, the applicant must obtain review and approval by an IRB that is established at the facility or site where the device is to be used or the local IRB must defer, in writing, to a similarly constituted IRB that has agreed to oversee such use. Absent IRB approval, the device cannot be administered to humans. The agency declines to limit the IRB's review or its functions in the manner suggested by the comment because IRB's have traditionally enjoyed considerable latitude in establishing their own operational procedures and reviews. FDA believes that the approval criteria set forth in the IRB regulations (21 CFR 56.111) can and should be interpreted to include consideration of the patient's need for the HUD and the likelihood that the device is appropriate for the patient's condition or disease state. For example, the regulations require that the IRB determine that the ''risks to subjects are reasonable in relation to anticipated benefits.'' Such a determination would necessarily require a balancing of patient need together with the probability of clinical benefit against the possible risks of using the device. In contrast, an IRB evaluating a HUD retains the discretion to minimize or ignore approval criteria that may be inappropriate in the treatment context (e.g., ''the importance of the knowledge that may be expected to result'').

FDA declines to adopt the suggestion that the IRB make semiannual

submissions to the holder of the HDE of ''all records of approvals for use of the humanitarian device.'' Section 814.124(a) requires the IRB to comply with the regulations in part 56 (21 CFR part 56), including provisions concerning continuing review and recordkeeping. Insofar as the holder of the approved HDE retains control over the shipment of the device, it has the discretion to require any reports from the IRB or the treating physician as a condition of the initial shipment of the device or future shipments.

Proposed § 812.30(d) and (e) FDA Action on Applications and Revocation of an Application for a HUD

Proposed § 812.30(d) and (e) described FDA action on HDE applications, and the agency received two comments on these sections.

22. One comment suggested amending the requirement that an application list the name, address, and chairperson of each IRB that has been or will be asked to review the investigation and a certification of the action taken by the IRB's. The comment asserted that requiring individual approval of each location where a clinical investigation would be conducted would deny timely access to HUD's. Alternatively, the comment suggested that FDA only approve the study protocol and a sample consent form, and that IRB's rather than FDA approve participation of each location. The sponsor would send information regarding additional study locations and IRB's to FDA every 18 months.

Because FDA has elected not to regulate HUD's as investigational devices subject to the requirements of part 812, the final regulation does not include any provision requiring the applicant to submit the name or address of any reviewing IRB. Nor will FDA review sample consent forms since informed consent is not being required by FDA. As discussed elsewhere in this notice, the HDE applicant is responsible for ensuring that the HUD is not used in the treatment or diagnosis of a patient prior to obtaining IRB approval from either the IRB at the health care facility or another IRB who has assumed that responsibility for the facility. Although IRB's are required to comply with the regulations in part 56, FDA will not require any reports from IRB's or HDE applicants other than those specified in part 56 and §§ 814.124 and 814.126.

23. The second comment suggested a new provision establishing strict timeframes for FDA review, criteria for approving, not approving, and withdrawing approval of an HDE application, and the factors and evidence FDA would consider in deciding whether the device would expose patients to an unreasonable or significant risk of illness or injury. For example, the comment would require FDA to notify applicants, in writing, when the agency receives an HDE application and would require FDA to approve the HDE application within 30 days of receipt or, if the agency did not approve the HDE application within 30 days, the application would be considered to be approved unless FDA requested additional information from the HDE applicant or denied approval within 30 days. The comment's suggested criteria for approving an HDE application paraphrased the statutory requirements at section 520(m)(2) of the act. The criteria the comment suggested for denying approval included the applicant's failure to comply with application or labeling requirements or, if nonclinical laboratory studies were involved, failure to comply with good laboratory practice requirements, a false statement of material fact, and the applicant's refusal to permit an authorized FDA employee to conduct an inspection. The comment would also create an administrative appeals mechanism to the ODE and later to the Office of the Center Director, CDRH for a decision not to approve an HDE application.

FDA agrees, in part, with the comment and has established specific timeframes for processing requests for HUD designation as well as for filing and reviewing HDE applications. Under § 814.102 of the final rule, a request for HUD designation will be reviewed within 45 days of receipt by OOPD. If the request for HUD designation is approved, this designation may be submitted or referenced in the HDE application (§ 814.104) which is submitted to ODE.

ODE will notify the applicant within 45 days of receiving an original HDE application or HDE supplement whether the application has been accepted for filing (see § 814.112). The criteria and procedures for filing an HDE are similar to those for PMA's. After filing an HDE or HDE supplement, § 814.114(a) requires that FDA take action on the application within 180 days from the date of receipt. (This time period includes the 45 days allotted to FDA under § 814.112 for making the filing decision.)

Although these time periods are longer than the 30 day IDE review period suggested by the comment, FDA believes that they are warranted. While HDE applications will not contain data intended to establish effectiveness, they will contain other information that is not included in PMA's under part 814. As discussed previously, therefore, the agency believes that 180 days will generally be required in order to review the information submitted in the HDE application and to make the determinations required by the statute (section 520(m)(2)(A) through (m)(2)(C)). By establishing intermediate steps in the submission and review process, the agency has attempted to ensure expeditious review of an HDE application, because only those applications that contain (or reference) a HUD designation and are complete enough to be filed will enter the review queue. In addition, FDA notes that there is nothing in the legislative history of section 520(m) of the act to suggest that Congress expected FDA to review marketing applications for HUD's within accelerated timeframes which would detract resources from reviews of other devices that may benefit larger populations. Furthermore, as discussed earlier, humanitarian use devices may meet the criteria for expedited review. In such cases, the agency will review these applications as quickly as possible.

The agency agrees with the comment's suggestion that criteria for the various actions FDA may take on an application should be incorporated into the final rule. Section 814.116 specifies the criteria for issuing an approval order, an approvable letter, or a not approvable letter, while § 814.118 specifies the criteria for issuing a denial or withdrawal of approval. These criteria are largely similar to the criteria for FDA action on a PMA and, thus, are consistent with those suggested by the comment.

The agency agrees with the comment that administrative appeal mechanisms should be provided. Thus, subpart H provides for such mechanisms by referencing § 814.42(d) for filing decisions and § 814.44 for not approvable letters.

Proposed § 812.38(e) Availability of Data and Information

24. Proposed § 812.38(e) would have maintained the confidentiality of data and information in an HDE application until final approval of the IDE application for the HUD. At that time, FDA would make publicly available information such as the identity of the device, the disease or condition to be treated, patient exclusion criteria, and the name, address, and phone number of a contact person for the sponsor. One comment suggested a new confidentiality provision that would be similar, but not identical, to the confidentiality provision for PMA's at

§ 814.9. The comment would essentially permit disclosure of information in an HDE application in accordance with the agency's regulations governing disclosure of information in a PMA application. The comment would permit disclosure of the existence of an application only if the application had been publicly disclosed or acknowledged, and, if the HDE application's existence had been publicly disclosed or acknowledged, restrict disclosures to summaries of portions of the safety data. If FDA approved the HDE application, the comment suggested that FDA could disclose the HDE application's existence and a detailed summary of the safety information, including any adverse event reports or consumer complaints, assay or analytical methods (unless otherwise protected as confidential or trade secret information), and all correspondence and written summaries of oral discussions. The comment would also permit disclosure of a summary of portions of the safety data before FDA approved the HDE application ''if disclosure is relevant to public consideration of a specific pending issue.''

Because the agency has moved the HDE provisions from the IDE regulations to the PMA regulations, FDA has created § 814.122 to address the confidentiality of data and information in an HDE application. Under § 814.122(a), the HDE application file consists of all data and information submitted with or incorporated by reference in the HDE application, any IDE incorporated into the HDE application, or any other related submission. Disclosure of any record contained in an HDE application file will be in accordance with part 20 (21 CFR part 20) and § 814.122. (In this final rule, the agency is amending part 20 to include a reference to HDE's.)

Section 814.122(b) states that HDE's shall be subject to the same restrictions and conditions regarding disclosure as are applied to PMA's under the provisions of § 814.9(b) through (h), as applicable. FDA has included ''as applicable'' in this provision, as in other provisions in subpart H, to signify that certain portions of the PMA regulations, namely those relating to the submission, review, or disclosure of effectiveness data, may not be applicable to HDE's. In accordance with § 814.9, the existence of an HDE file or data and information in the file may not be disclosed by FDA unless the existence of the file has been publicly disclosed or acknowledged. Also, if the existence of the HDE file has been publicly disclosed or acknowledged before an order approving or denying approval issued, data and information in the file are not available for disclosure. Once FDA has issued an approval order or an order denying approval of an application, FDA will make available to the public the fact of the existence of the HDE and a detailed summary of information submitted to FDA respecting the safety of the device and the basis for the order. Information such as safety data, test or study protocols, adverse event reports, product experience reports, consumer complaints or similar information, lists of components previously disclosed to the public, assay methods or analytical methods, and all correspondence and written summaries of oral discussions related to the HDE file, in accordance with the provisions of § 814.9(e) also become available for public disclosure. Finally, FDA may disclose a summary of portions of the safety data before an approval order or an order denying approval of the HDE issues, if disclosure is relevant to public consideration of a pending issue and, in accordance with § 814.9(g), other information contained in an HDE becomes available under the particular circumstances set forth in that provision.

Proposed § 812.39 Certification

25. Proposed § 812.39 would have required sponsors to certify that the data and information submitted to the agency are true and accurate.

FDA received no comments on this provision but has reconsidered the need for it. As provided for in §§ 814.42 and 814.45 for PMA's, subpart H includes provisions that would permit FDA to not file, deny approval, or withdraw approval of an HDE application if the agency determines that the application contained a false statement of material fact. Therefore, the agency has concluded that a certification as to the truthfulness and accuracy of the information submitted in an application is not needed.

Limitations on Charging

26. One comment suggested that, because the original proposed rule included a prohibition against commercialization, a provision should be added to insulate HDE holders from charges of commercialization in the event that they earned ''incidental profits which exceed its good faith estimates of costs.''

To address the cost issue, the final rule requires a report by an independent certified public accountant, made in accordance with the Statement on Standards for Attestation established by the American Institute of Certified Public Accountants, verifying that the amount charged will not exceed the costs of the device's research, development, fabrication, and distribution. The statute does not create an exemption for ''incidental profits.'' FDA believes that a report made in accordance with the requirements stated above should provide adequate assurance to both the HDE holder and the agency that the amount being charged does not violate section 520(m)(3) of the act. This requirement is also consistent with the cost verification procedures required for orphan drugs under 21 CFR 316.21(c)(8). However, as suggested by the Conference Report on the SMDA, an applicant will not be considered in violation of this provision if it receives incidental profits which exceed its good faith estimates of costs (H. Conf. Rept. at 28).

IV. Analysis of Impacts

FDA has examined the impacts of the final rule under Executive Order 12866 and the Regulatory Flexibility Act (Pub. L. 96–354). Executive Order 12866 directs agencies to assess all costs and benefits 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 rule is consistent with the regulatory philosophy and principles identified in the Executive Order. In addition, the final rule is not a significant regulatory action as defined by the Executive Order and so is not subject to review under the Executive Order.

The Regulatory Flexibility Act requires agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities. Because the final rule reduces the requirements imposed on firms conducting research and development activities on devices intended for use in diagnosing or treating small populations, the agency certifies that the final rule will not have a significant economic impact on a substantial number of small entities. Therefore, under the Regulatory Flexibility Act, no further analysis is required.

V. Environmental Impact

The agency has determined under 21 CFR 25.24(a)(8) 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.

VI. Paperwork Reduction Act of 1995

This final rule contains information collections which are subject to review by OMB under the Paperwork Reduction Act of 1995 (Pub. L. 104–13). The title, description, and respondent description of the information collections are shown below with an estimate of the annual recordkeeping and periodic 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 the collection of information.

Title: Medical Devices; Humanitarian Use Devices.

Description: This regulation implements the provision of the SMDA regarding HUD's. A HUD is exempt from the effectiveness requirements of sections 514 and 515 of the act. In order to implement this exemption, FDA is amending the premarket approval regulations in part 814 by creating new subpart H. This final regulation prescribes the procedures for submitting HDE applications, amendments, and supplements; procedures for obtaining an extension of the exemption; and the criteria for FDA review and approval of HDE's. This final rule will create a needed incentive for the development of devices for use in the treatment or diagnosis of diseases or conditions affecting a small number of individuals.

Description of Respondents: Businesses or other for profit organizations.

ESTIMATED ANNUAL REPORTING BURDEN

21 CFR Section	No. of Respondents	Annual Frequency per Response	Total Annual Responses	Hours per Response	Total Hours
814.102	20	1	20	40	800
814.104	15	1	15	320	4,800
814.106	10	1	10	120	1,200
814.108	12	1	12	80	960
814.110(a)	1	1	1	80	80
814.112(b)	1	1	1	8	8
814.116(b)	12	1	12	8	96
814.118(d)	1	1	1	8	8
814.120(b)	10	1	10	200	2,000
814.124(b)	2	1	2	2	4
814.126(b)(i)	2	1	2	120	240
TOTAL					10,196

ESTIMATED ANNUAL RECORDKEEPING BURDEN

21 CFR Section	No. of Recordkeepers	Annual Frequency per Recordkeeping	Total Annual Records	Hours per Recordkeeper	Total Hours
814.126(b)(ii)	12	1	12	2	24
Total					24

There are no operating and maintenance costs or capitol costs associated with this information collection.

Although the December 21, 1992, proposed rule provided a 60-day comment period under the Paperwork Reduction Act of 1980, and this final rule is based on the comments received, as required by 44 U.S.C. section 3507(d), FDA is providing additional opportunities for public comment under the Paperwork Reduction Act of 1995, which applies to this final rule and was enacted after the expiration of the comment period. Organizations and individuals wishing to submit comments regarding these burden estimates or any aspect of these information collection requirements should do so by August 26, 1996. These comments should be directed to FDA's Dockets Management Branch (address above). FDA particularly invites comments on: (1) Whether the proposed collection of information is necessary for the proper performance of the functions of the agency, including whether the information will have practical utility; (2) the accuracy of the agency'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 those who are to respond, including through the use of automated collection techniques, when appropriate, and other forms of information technology.

At the close of the 60-day comment period, FDA will review the comments received, make revisions as necessary to the information collection requirements, and submit the requirements to OMB for review and approval. Additional time will be allotted for public comment to OMB on the requirements and OMB review. Prior to the effective date of this final rule, FDA will publish a notice in the Federal Register of OMB's decision to approve, modify, or disapprove the information collection requirements. 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

21 CFR Part 20

Confidential business information, Courts, Freedom of information, Government employees.

21 CFR Part 814

Administrative practice and procedure, Confidential business information, 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 parts 20 and 814 are amended as follows:

PART 20—PUBLIC INFORMATION

1. The authority citation for 21 CFR part 20 continues to read as follows:

Authority: Secs. 201–903 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321–393); secs. 301, 302, 303, 307, 310, 311, 351, 352, 354–360F, 361, 362, 1701–1706, 2101 of the Public Health Service Act (42 U.S.C. 241, 242, 242a, 242l, 242n, 243, 262, 263, 263b–263n, 264, 265, 300u–300u–5, 300aa–1); 5 U.S.C. 552; 18 U.S.C. 1905; 19 U.S.C. 2531–2582; 21 U.S.C. 1401–1403.

2. Section 20.100 is amended by adding new paragraph (c)(41) to read as follows:

§ 20.100 Applicability; cross-reference to other regulations.

* * * * *

(c) * * *

(41) Humanitarian device exemption application, in § 814.122 of this chapter.

PART 814—PREMARKET APPROVAL OF MEDICAL DEVICES

3. The authority citation for 21 CFR part 814 continues to read as follows:

Authority: Secs. 501, 502, 503, 510, 513–520, 701, 702, 703, 704, 705, 708, 721, 801 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 351, 352, 353, 360, 360c–360j, 371, 372, 373, 374, 375, 379, 379e, 381).

4. Section 814.3 is amended by adding new paragraphs (m) and (n) to read as follows:

§ 814.3 Definitions.

* * * * *

(m) *HDE* means a premarket approval application submitted pursuant to this subpart seeking a humanitarian device exemption from the effectiveness requirements of sections 514 and 515 of the act as authorized by section 520(m)(2) of the act.

(n) *HUD* (humanitarian use device) means a medical device intended to benefit patients in the treatment or diagnosis of a disease or condition that affects or is manifested in fewer than 4,000 individuals in the United States per year.

5. New subparts F and G are added and reserved and subpart H, consisting of §§ 814.100 through 814.126, is added to read as follows:

Subpart H—Humanitarian Use Devices

Sec.

814.100 Purpose and scope.
814.102 Designation of HUD status.
814.104 Original applications.
814.106 HDE amendments and resubmitted HDE's.
814.108 Supplemental applications.
814.110 New indications for use.
814.112 Filing an HDE.
814.114 Timeframes for reviewing an HDE.
814.116 Procedures for review of an HDE.
814.118 Denial of approval or withdrawal of approval of an HDE.
814.120 Requests for extension.
814.122 Confidentiality of data and information.
814.124 Institutional Review Board requirements.
814.126 Postapproval requirements and reports.

Subpart H—Humanitarian Use Devices

§ 814.100 Purpose and scope.

(a) This subpart H implements section 520(m) of the act. The purpose of section 520(m) is, to the extent consistent with the protection of the public health and safety and with ethical standards, to encourage the discovery and use of devices intended to benefit patients in the treatment or diagnosis of diseases or conditions that affect or are manifested in fewer than 4,000 individuals in the United States per year. This subpart provides procedures for obtaining:

(1) HUD designation of a medical device; and

(2) Temporary marketing approval for the HUD notwithstanding the absence of reasonable assurance of effectiveness that would otherwise be required under sections 514 and 515 of the act.

(b) Although a HUD may also have uses that differ from the humanitarian use, applicants seeking approval of any non-HUD use shall submit a PMA as required under § 814.20, or a premarket notification as required under part 807 of this chapter.

(c) Obtaining marketing approval for a HUD involves two steps:

(1) Obtaining designation of the device as a HUD from FDA's Office of Orphan Products Development, and

(2) Submitting an HDE to the Office of Device Evaluation (ODE), Center for Devices and Radiological Health (CDRH).

(d) The approval by ODE of an HDE under this subpart H shall be effective for a period of 18 months from the date of the approval letter, and shall permit the applicant to market the HUD in the United States in accordance with the restrictions described in this subpart H. Extensions of the approval may be granted in accordance with this subpart H.

§ 814.102 Designation of HUD status.

(a) *Request for designation*. Prior to submitting an HDE application, the applicant shall submit a request for HUD designation to FDA's Office of Orphan Products Development. The request shall contain the following:

(1) A statement that the applicant requests HUD designation for a rare disease or condition or a valid subset of a disease or condition which shall be identified with specificity;

(2) The name and address of the applicant, the name of the applicant's primary contact person and/or resident agent, including title, address, and telephone number;

(3) A description of the rare disease or condition for which the device is to be used, the proposed indication or indications for use of the device, and the reasons why such therapy is needed. If the device is proposed for an indication that represents a subset of a common disease or condition, a demonstration that the subset is medically plausible should be included;

(4) A description of the device and a discussion of the scientific rationale for the use of the device for the rare disease or condition; and

(5) Documentation, with appended authoritative references, to demonstrate that the device is designed to treat or diagnose a disease or condition that affects or is manifested in fewer than 4,000 people in the United States per year. If the device is for diagnostic purposes, the documentation must demonstrate that fewer than 4,000 patients per year would be subjected to diagnosis by the device in the United States. Authoritative references include literature citations in specialized medical journals, textbooks, specialized medical society proceedings, or governmental statistics publications. When no such studies or literature citations exist, the applicant may be able to demonstrate the prevalence of the disease or condition in the United States by providing credible conclusions from appropriate research or surveys.

(b) *FDA action*. Within 45 days of receipt of a request for HUD designation, FDA will take one of the following actions:

(1) Approve the request and notify the applicant that the device has been designated as a HUD based on the information submitted;

(2) Return the request to the applicant pending further review upon submission of additional information. This action will ensue if the request is incomplete because it does not on its face contain all of the information required under § 814.102(a). Upon receipt of this additional information, the review period may be extended up to 45 days; or

(3) Disapprove the request for HUD designation based on a substantive review of the information submitted. FDA may disapprove a request for HUD designation if:

(i) There is insufficient evidence to support the estimate that the disease or condition for which the device is

designed to treat or diagnose affects or is manifested in fewer than 4,000 people in the United States per year;

(ii) FDA determines that, for a diagnostic device, 4,000 or more patients in the United States would be subjected to diagnosis using the device per year; or

(iii) FDA determines that the patient population defined in the request is not a medically plausible subset of a larger population.

(c) *Revocation of designation*. FDA may revoke a HUD designation if the agency finds that:

(1) The request for designation contained an untrue statement of material fact or omitted material information; or

(2) Based on the evidence available, the device is not eligible for HUD designation.

(d) *Submission*. The applicant shall submit two copies of a completed, dated, and signed request for HUD designation to: Office of Orphan Products Development (HF–35), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857.

§ 814.104 Original applications.

(a) *United States applicant or representative*. The applicant or an authorized representative shall sign the HDE. If the applicant does not reside or have a place of business within the United States, the HDE shall be countersigned by an authorized representative residing or maintaining a place of business in the United States and shall identify the representative's name and address.

(b) *Time for submission*. An original HDE may only be submitted to the agency between October 24, 1996, and April 27, 2001, unless otherwise permitted by statute.

(c) *Contents*. Unless the applicant justifies an omission in accordance with paragraph (d) of this section, an HDE shall include:

(1) A copy of or reference to the determination made by FDA's Office of Orphan Products Development (in accordance with § 814.102) that the device qualifies as a HUD;

(2) An explanation of why the device would not be available unless an HDE were granted and a statement that no comparable device (other than another HUD approved under this subpart or a device under an approved IDE) is available to treat or diagnose the disease or condition. The application also shall contain a discussion of the risks and benefits of currently available devices or alternative forms of treatment in the United States;

(3) An explanation of why the probable benefit to health from the use of the device outweighs the risk of injury or illness from its use, taking into account the probable risks and benefits of currently available devices or alternative forms of treatment. Such explanation shall include a description, explanation, or theory of the underlying disease process or condition, and known or postulated mechanism(s) of action of the device in relation to the disease process or condition;

(4) All of the information required to be submitted under § 814.20(b), except that:

(i) In lieu of the summaries, conclusions, and results from clinical investigations required under §§ 814.20(b)(3)(v)(B), (b)(3)(vi), and (b)(6)(ii), the applicant shall include the summaries, conclusions, and results of all clinical experience or investigations (whether adverse or supportive) reasonably obtainable by the applicant that are relevant to an assessment of the risks and probable benefits of the device; and

(ii) In addition to the proposed labeling requirement set forth in § 814.20(b)(10), the labeling shall bear the following statement: Humanitarian Device. Authorized by Federal law for use in the [treatment or diagnosis] of [specify disease or condition]. The effectiveness of this device for this use has not been demonstrated; and

(5) The amount to be charged for the device and a report by an independent certified public accountant, made in accordance with the Statement on Standards for Attestation established by the American Institute of Certified Public Accountants, verifying that the amount charged does not exceed the costs of the device's research, development, fabrication, and distribution.

(d) *Omission of information*. If the applicant believes that certain information required under paragraph (c) of this section is not applicable to the device that is the subject of the HDE, and omits any such information from its HDE, the applicant shall submit a statement that identifies and justifies the omission. The statement shall be submitted as a separate section in the HDE and identified in the table of contents. If the justification for the omission is not accepted by the agency, FDA will so notify the applicant.

(e) *Address for submissions and correspondence*. Copies of all original HDE's, amendments, supplements, and requests for extension, as well as any correspondence relating to an HDE, shall be sent or delivered to the Document Mail Center (HFZ–401), Office of Device Evaluation, Center for Devices and Radiological Health, Food and Drug Administration, 9200 Corporate Blvd., Rockville, MD 20850.

§ 814.106 HDE amendments and resubmitted HDE's.

An HDE or HDE supplement may be amended or resubmitted upon an applicant's own initiative, or at the request of FDA, for the same reasons and in the same manner as prescribed for PMA's in § 814.37. The timeframes and extension of review times set forth in § 814.37 for PMA's shall also be applicable to HDE's.

§ 814.108 Supplemental applications.

After FDA approval of an original HDE, an applicant shall submit supplements in accordance with the requirements for PMA's under § 814.39, except that a request for a new indication for use of a HUD shall comply with the requirements set forth in § 814.110.

§ 814.110 New indications for use.

(a) An applicant seeking a new indication for use of a HUD approved under this subpart H shall obtain a new designation of HUD status in accordance with § 814.102 and shall submit an original HDE in accordance with § 814.104.

(b) An application for a new indication for use made under § 814.104 may incorporate by reference any information or data previously submitted to the agency under an HDE.

§ 814.112 Filing an HDE.

(a) The filing of an HDE means that FDA has made a threshold determination that the application is sufficiently complete to permit substantive review. Within 45 days from the date an HDE is received by FDA, the agency will notify the applicant whether the application has been filed. FDA may refuse to file an HDE if any of the following applies:

(1) The application is incomplete because it does not on its face contain all the information required under § 814.104(c);

(2) FDA determines that there is a comparable device available (other than another HUD approved under this subpart or a device under an approved IDE) to treat or diagnose the disease or condition for which approval of the HUD is being sought; or

(3) The application contains an untrue statement of material fact or omits material information.

(b) The provisions contained in § 814.42(b), (c), and (d) regarding notification of filing decisions, filing dates, the start of the 180-day review

period, and applicant's options in response to FDA refuse to file decisions shall apply to HDE's submitted under this subpart as well as to PMA's submitted under § 814.20.

§ 814.114 Timeframes for reviewing an HDE.

Within 180 days after receipt of an HDE that is accepted for filing and to which the applicant does not submit a major amendment, FDA will send the applicant an approval order, an approvable letter, or a not approvable letter (under § 814.116), or an order denying approval (under § 814.118).

§ 814.116 Procedures for review of an HDE.

(a) *Substantive review*. FDA will begin substantive review of an HDE after the HDE is accepted for filing under § 814.112. FDA may refer an original HDE application to a panel on its own initiative, and shall do so upon the request of an applicant, unless FDA determines that the application substantially duplicates information previously reviewed by a panel. If the HDE is referred to a panel, the agency shall follow the procedures set forth under § 814.44.

(b) *Approval order*. FDA will issue to the applicant an order approving an HDE if none of the reasons in § 814.118 for denying approval of the application applies. FDA will approve an application on the basis of draft final labeling if the only deficiencies in the application concern editorial or similar minor deficiencies in the draft final labeling. Such approval will be conditioned upon the applicant incorporating the specified labeling changes exactly as directed and upon the applicant submitting to FDA a copy of the final printed labeling before marketing. The notice of approval of an HDE will be published in the Federal Register in accordance with the rules and policies applicable to PMA's submitted under § 814.20. Following the issuance of an approval order, data and information in the HDE file will be available for public disclosure in accordance with § 814.9(b) through (h), as applicable.

(c) *Approvable letter*. FDA will send the applicant an approvable letter if the application substantially meets the requirements of this subpart and the agency believes it can approve the application if specific additional information is submitted or specific conditions are agreed to by the applicant. The approvable letter will describe the information FDA requires to be provided by the applicant or the conditions the applicant is required to meet to obtain approval. For example, FDA may require as a condition to approval:

(1) The submission of certain information identified in the approvable letter, e.g., final labeling;

(2) Restrictions imposed on the device under section 520(e) of the act;

(3) Postapproval requirements as described in subpart E of this part; and

(4) An FDA inspection that finds the manufacturing facilities, methods, and controls in compliance with part 820 of this chapter and, if applicable, that verifies records pertinent to the HDE.

(d) *Not approvable letter*. FDA will send the applicant a not approvable letter if the agency believes that the application may not be approved for one or more of the reasons given in § 814.118. The not approvable letter will describe the deficiencies in the application and, where practical, will identify measures required to place the HDE in approvable form. The applicant may respond to the not approvable letter in the same manner as permitted for not approvable letters for PMA's under § 814.44(f).

§ 814.118 Denial of approval or withdrawal of approval of an HDE.

(a) FDA may deny approval or withdraw approval of an application if the applicant fails to meet the requirements of section 520(m) of the act or of this part, or of any condition of approval imposed by an IRB or by FDA, or any postapproval requirements imposed under § 814.126. In addition, FDA may deny approval or withdraw approval of an application if, upon the basis of the information submitted in the HDE or any other information before the agency, FDA determines that:

(1) There is a lack of a showing of reasonable assurance that the device is safe under the conditions of use prescribed, recommended, or suggested in the labeling thereof;

(2) The device is ineffective under the conditions of use prescribed, recommended, or suggested in the labeling thereof;

(3) The applicant has not demonstrated that there is a reasonable basis from which to conclude that the probable benefit to health from the use of the device outweighs the risk of injury or illness, taking into account the probable risks and benefits of currently available devices or alternative forms of treatment;

(4) The application or a report submitted by or on behalf of the applicant contains an untrue statement of material fact, or omits material information;

(5) The device's labeling does not comply with the requirements in part 801 or part 809 of this chapter;

(6) A nonclinical laboratory study that is described in the HDE and that is essential to show that the device is safe for use under the conditions prescribed, recommended, or suggested in its proposed labeling, was not conducted in compliance with the good laboratory practice regulations in part 58 of this chapter and no reason for the noncompliance is provided or, if it is, the differences between the practices used in conducting the study and the good laboratory practice regulations do not support the validity of the study;

(7) Any clinical investigation involving human subjects described in the HDE, subject to the institutional review board regulations in part 56 of this chapter or the informed consent regulations in part 50 of this chapter, was not conducted in compliance with those regulations such that the rights or safety of human subjects were not adequately protected;

(8) The applicant does not permit an authorized FDA employee an opportunity to inspect at a reasonable time and in a reasonable manner the facilities and controls, and to have access to and to copy and verify all records pertinent to the application; and

(9) The device's HUD designation should be revoked in accordance with § 814.102(c).

(b) If FDA issues an order denying approval of an application, the agency will comply with the same notice and disclosure provisions required for PMA's under § 814.45(b) and (d), as applicable.

(c) FDA will issue an order denying approval of an HDE after an approvable or not approvable letter has been sent and the applicant:

(1) Submits a requested amendment but any ground for denying approval of the application under § 814.118(a) still applies;

(2) Notifies FDA in writing that the requested amendment will not be submitted; or

(3) Petitions for review under section 515(d)(3) of the act by filing a petition in the form of a petition for reconsideration under § 10.33 of this chapter.

(d) Before issuing an order withdrawing approval of an HDE, FDA will provide the applicant with notice and an opportunity for a hearing as required for PMA's under § 814.46(c) and (d), and will provide the public with notice in accordance with § 814.46(e), as applicable.

(e) Unless FDA otherwise determines that continued marketing under the

HDE is inconsistent with the intent of section 520(m) of the act, FDA will not withdraw approval of an HDE solely because it is subsequently determined that the disease or condition for which the HUD is intended affects or is manifested in more than 4,000 people in the United States per year. However, this fact may serve as a basis for disapproving an extension request.

§ 814.120 Requests for extension.

(a) *Eligibility*. In response to a request by the holder of an HDE, FDA may extend the HDE for an additional 18-month term. An exemption may be extended more than once, and may be extended after the expiration of the 5-year period that began on October 24, 1996, as provided by section 520(m)(5) of the act. If the approval term for an HDE has lapsed, the HDE is ineligible for extension under this section and the applicant must cease marketing the device until a new HDE has been submitted and approved in accordance with this part.

(b) *Submission*. In order to avoid the risk of a lapse in marketing approval, the holder of an HDE wishing to obtain an extension shall submit such a request to FDA at least 90 days prior to the expiration of the HDE. A request for extension must be submitted in writing, together with a new, separately bound, request for HUD designation. The request for extension and the request for HUD designation shall be submitted to the Office of Device Evaluation, CDRH at the address specified for the submission of original HDE's (§ 814.104(e)), and the outside envelope should be plainly marked: ''Request for Extension of HDE Approval.'' The submission shall state the applicant's name and address, the HDE number, and shall include the following information based upon the first 12 months of experience with the device following the most recent HDE approval or extension:

(1) An update of the information required under § 814.102(a) in a separately bound volume;

(2) An update of the information required under §§ 814.104(c)(2), (c)(3),and (c)(5);

(3) The number of devices that have been shipped or sold since initial marketing approval under this subpart and, if the number shipped or sold exceeds 4,000, an explanation and estimate of the number of devices used per patient. If a single device is used on multiple patients, the applicant shall submit an estimate of the number of patients treated or diagnosed using the device together with an explanation of the basis for the estimate;

(4) Information describing the applicant's clinical experience with the device since the HDE was initially approved. This shall include safety information that is known or reasonably should be known to the applicant, medical device reports made pursuant to part 803 of this chapter, any data generated from postmarketing studies, and information (whether published or unpublished) that is known or reasonably expected to be known by the applicant that may affect an evaluation of the safety of the device or that may affect the statement of contraindications, warnings, precautions, and adverse reactions in the device labeling; and

(5) A summary of any changes made to the device in accordance with supplements submitted under § 814.108.

(c) *Action*. Within 90 days of receipt of a request for an extension of an HDE that is submitted in accordance with this section, FDA will send the applicant either an approval order, approvable letter, a not approvable letter, or an order denying approval, applying the same criteria under this subpart as are applicable to the original HUD designation and HDE application. The effective date of an extension shall be the day the extension was granted or the day following the last effective day of the original HDE approval or the most recent extension, whichever is later. An extension request not acted upon by FDA within 90 days shall be deemed approved.

(d) *Waiver of final report*. An HDE holder seeking a request for extension under this section is exempt from the requirement of submitting a final report under § 814.126(b).

§ 814.122 Confidentiality of data and information.

(a) *Requirement for disclosure*. The ''HDE file'' includes all data and information submitted with or referenced in the HDE, any IDE incorporated into the HDE, any HDE amendment or supplement, any report submitted under § 814.126, any master file, or any other related submission. Any record in the HDE file will be available for public disclosure in accordance with the provisions of this section and part 20 of this chapter.

(b) *Extent of disclosure*. Disclosure by FDA of the existence and contents of an HDE file shall be subject to the same rules that pertain to PMA's under § 814.9(b) through (h), as applicable.

§ 814.124 Institutional Review Board requirements.

(a) *IRB approval*. The HDE holder is responsible for ensuring that a HUD approved under this subpart is administered only in facilities having an Institutional Review Board (IRB) constituted and acting pursuant to part 56 of this chapter, including continuing review of use of the device. In addition, a HUD may be administered only if such use has been approved by the IRB located at the facility or by a similarly constituted IRB that has agreed to oversee such use and to which the local IRB has deferred in a letter to the HDE holder, signed by the IRB chair or an authorized designee.

(b) *Withdrawal of IRB approval*. A holder of an approved HDE shall notify FDA of any withdrawal of approval for the use of a HUD by a reviewing IRB within 5 working days after being notified of the withdrawal of approval.

§ 814.126 Postapproval requirements and reports.

(a) An HDE approved under this subpart H shall be subject to the postapproval requirements and reports set forth under subpart E of this part, as applicable. In addition, medical device reports submitted to FDA in compliance with the requirements of part 803 of this chapter shall also be submitted to the IRB of record.

(b) In addition to the reports required under subpart E of this part, the holder of an approved HDE shall prepare and submit the following complete, accurate, and timely reports:

(1) *Final report*. Unless a request for extension is submitted in accordance with § 814.120, a final report shall be submitted no later than 90 days following the expiration of the period of marketing approval. The final report shall include: An estimate of the number of patients who were treated or diagnosed with the device and the number of devices shipped or sold since initial marketing approval under this subpart H. (If the number of devices shipped or sold exceeds 4,000 per year, an explanation and estimate of the number of devices used per patient shall be included. Similarly, if a single device is used on multiple patients, the applicant shall submit an estimate of the number of patients treated or diagnosed using the device together with an explanation of the basis for the estimate.) The holder of the HDE shall also report information regarding retrieval or disabling of unused devices, a summary of results and conclusions with regard to clinical use of the device, and a summary of the medical device reports submitted under part 803 of this chapter. The report shall also contain a summary and bibliography of published and unpublished data, reports, and studies involving the device that are

known to or that reasonably should be known to the applicant and were not previously submitted to FDA. If, after reviewing the summary and bibliography, FDA concludes that FDA needs a copy of the unpublished or published information, FDA will notify the applicant that copies shall be submitted.

(2) *Other*. An HDE holder shall, for the duration of the period that a HUD is approved for marketing, maintain records of the names and addresses of the facilities to which the HUD has been shipped, correspondence with reviewing IRB's, as well as any other information requested by a reviewing IRB or FDA.

Dated: June 14, 1996.

William B. Schultz,

Deputy Commissioner for Policy.

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