

## Subpart H--Humanitarian Use Devices

As of June 14, 1996

### Sec. 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.

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### Sec. 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 Sec. 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.

## **Sec. 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 Sec. 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.

### **Sec. 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 Sec. 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 Sec. 814.20(b), except that:-
- i) In lieu of the summaries, conclusions, and results from clinical investigations required under Secs. 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 Sec. 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.

### **Sec. 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 Sec. 814.37. The timeframes and extension of review times set forth in Sec. 814.37 for PMA's shall also be applicable to HDE's.

### **Sec. 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 Sec. 814.39, except that a request for a new indication for use of a HUD shall comply with the requirements set forth in Sec. 814.110.

### **Sec. 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 Sec. 814.102 and shall submit an original HDE in accordance with Sec. 814.104.
- b) An application for a new indication for use made under Sec. 814.104 may incorporate by reference any information or data previously submitted to the agency under an HDE.

### **Sec. 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 Sec. 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 Sec. 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 Sec. 814.20.

### **Sec. 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 Sec. 814.116), or an order denying approval (under Sec. 814.118).

### **Sec. 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 Sec. 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 Sec. 814.44.
- b) Approval order. FDA will issue to the applicant an order approving an HDE if none of the reasons in Sec. 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 Sec. 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 Sec. 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 Sec. 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 Sec. 814.44(f).

### **Sec. 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 Sec. 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 Sec. 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 Sec. 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 Sec. 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 Sec. 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 Sec. 814.46(c) and (d), and will provide the public with notice in accordance with Sec. 814.46(e), as applicable.
- d) erased in error
- 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. -

### **Sec. 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 (Sec. 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 Sec. 814.102(a) in a separately bound volume;
  - 2) An update of the information required under Secs. 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 Sec. 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 Sec. 814.126(b).

### **Sec. 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 Sec. 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 Sec. 814.9(b) through (h), as applicable.

### **Sec. 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.

### **Sec. 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 Sec. 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.