# Guidance for Industry

# Providing Regulatory Submissions in Electronic Format — Orphan-Drug and Humanitarian Use Device Designation Requests and Related Submissions

*DRAFT GUIDANCE*

**This guidance document is being distributed for comment purposes only.**

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document send an e-mail to james.bona@fda.hhs.gov or contact James D. Bona, 301-827-0978.

**U.S. Department of Health and Human Services**
**Food and Drug Administration**
**Office of Orphan Products Development (OPD)**
**February 2006**
**Electronic Submissions**

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*Additional copies are available at:*

http://www.fda.gov/orphan/esub/esub.htm

**U.S. Department of Health and Human Services**
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# Guidance for Industry
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This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

## I. INTRODUCTION

This is one in a series of guidance documents intended to assist sponsors making regulatory submissions to the Office of Orphan Products Development (OPD) in electronic format using the FDA Electronic Submissions Gateway (ESG) pathway or directly to OPD on physical media (e.g., CD-ROMs). This guidance discusses issues related to the electronic submission of requests for orphan-drug designation, humanitarian use device designation (HUD), and related submissions.

The goals of this guidance are to enhance the receipt, processing, review, and archiving of electronic submissions to OPD.

In October 2003, the Food and Drug Administration (FDA) issued the draft guidance for industry *Providing Regulatory Submissions in Electronic Format — General Considerations*. The *General Considerations Guidance* discusses issues common to all types of electronic regulatory submissions, such as acceptable file formats, physical media and submission procedures.[1] As set forth under Part 11, Title 21, Code of Federal Regulations, for records submitted to the FDA, sponsors may elect to use electronic records in lieu of paper records, in whole or part, provided the requirements of Part 11 are met and the documents or parts of documents to be submitted have been identified by the FDA in public docket No. 92S-0251 (http://www.fda.gov/ohrms/dockets/dockets/92s0251/92s0251.htm) as being the type of submission it is prepared to accept in electronic format.[2]

[1] This October 2003 draft guidance is a revision of the *General Considerations Guidance of 1999; the revision was* issued as a draft guidance for public comment in October 2003, and it is available at http://www.fda.gov/cder/guidance/4156dft.pdf.

[2] For a discussion of the Agency's perspectives on 21 CFR part 11, see the guidance for industry *Part 11, Electronic Records; Electronic Signatures — Scope and Application*, which issued in September 2003 (http://www.fda.gov/cder/guidance/5667fnl.pdf)

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

### A. Scope

This guidance applies to orphan-drug and humanitarian use device (HUD) designation requests to OPD as well as related submissions such as amendments, correspondence, and annual reports.

### B. Electronic Submissions

There are two ways you can provide electronic submissions to OPD. The first and preferred way is completely electronic through the FDA Electronic Submissions Gateway. Alternatively, you may send the submission directly to OPD on physical media with a signed paper cover letter.

We believe it is most beneficial to begin your electronic submissions with the initial submission of a request for an orphan drug or HUD designation. However, if you wish to make electronic submissions to previously submitted requests, please contact OPD first. You should avoid the submission of any paper documents when you follow the recommendations in this document except for the signed cover letter that accompanies submissions of physical media directly to OPD. You should submit the electronic information for all files following the specifications associated with this guidance.

Once you begin to submit a specific request in electronic format based on this guidance, subsequent submissions to the request should continue to be submitted electronically.

### C. Document Information for Previous Submissions

If you have submitted a request for designation in paper form and decide to submit subsequent related requests (e.g., amendments, correspondence, annual reports) in electronic format based on this guidance, we do not expect you to provide electronic files for the previous submissions to the request. For example, if you submitted an original request in 2001 and now submit an amendment to the request electronically, we do not expect you to electronically re-submit the document information for the files submitted in 2001.

## II. ELECTRONIC SUBMISSIONS USING THE FDA GATEWAY (ESG)

### A. General Issues

The Food and Drug Administration (FDA) Electronic Submissions Gateway is an Agency-wide solution for accepting electronic regulatory submissions. The FDA ESG enables the secure submission of regulatory information for review. The FDA ESG will enable the FDA to process regulatory information automatically while it functions as:

- A single point of entry for the receipt and processing of all electronic submissions in a highly secure environment that complies with secure messaging standards
- A mechanism for automating current electronic processes such as the electronic acknowledgment of submissions

The electronic submission process encompasses the receipt, acknowledgment of receipt (to the sender), routing, and notification to a receiving Center or Office of the delivery of an electronic submission.

The FDA ESG is the central transmission point for sending information electronically to the FDA. Within that context, the FDA ESG is a conduit, or "highway", along which submissions travel to reach their final destination. It does not open or review submissions; it automatically routes them to the proper FDA Center or Office, in this case, the Office of Orphan Products Development.

### B. FDA ESG Preparation, Registration and Policy

There are a number of preparatory activities that should be completed before beginning the registration process. There are also system hardware and software considerations to ensure compatibility with and security for users of the FDA ESG. Access the internet webpage http://www.fda.gov/esg/ for all the information on FDA electronic submission gateway preparation, registration, and policies. Questions regarding the process can be directed to: esgprep@fda.gov.

Once registration has been completed and a digital certificate has been issued to serve as an electronic signature for the sponsor, submissions to OPD through the ESG should follow the format outlined in Part IV. OTHER INFORMATION ABOUT ELECTRONIC SUBMISSIONS. Questions regarding the format of electronic submissions should be directed to the electronic submission coordinator for orphan-drug designation requests at desigesub@fda.hhs.gov or for HUD designation requests at hudesub@fda.hhs.gov .

## III. ELECTRONIC SUBMISSIONS USING PHYSICAL MEDIA (E.G. CD-ROMS)

A second option for the electronic submission of documents to FDA is via physical media sent directly to OPD. This option is completely separate from the ESG.

Physical media should be submitted 1) as described in the *General Considerations Guidance* (http://www.fda.gov/cder/guidance/4156dft.pdf); 2) protected (e.g., in a sleeve, jewel case, physical media mailer); and 3) be attached securely to a jacket (e.g., notebook, binder).

The jacket should include a signed paper copy of the cover letter for the submission and the electronic media for archiving. Note in the cover letter that the submission is in electronic format and is virus free with a description of the software (name, version, and company) used to check the files for viruses.

Each unit of physical media and its jacket should be labeled with the following:

- Orphan-Drug Designation or Humanitarian Use Device Designation Request
- Designation Request # (e.g., D061234 for drugs or H061234 for devices, if known)
- Company Name
- Drug or Device Name
- Submission Type (original, amendment, annual report, or correspondence)
- Submission Date
- Disk/CD-ROM (total number submitted, i.e., # of #)
- Point of Contact for the Electronic Submission (name and telephone number)

A jacket can contain more than one unit of physical medium. If more than one unit of physical medium is contained in the jacket, the label on the jacket should include the number of units of physical media in the jacket (e.g., "Jacket contains 2 CD-ROMs"), and each unit of the physical media should be numbered in series as appropriate (e.g., "1 of 2," "2 of 2").

You can direct questions to OPD regarding the preparation of physical media electronic submissions for orphan-drug designation requests at desigesub@fda.hhs.gov or for humanitarian use device designation requests at hudesub@fda.hhs.gov or 301-827-3666.

These physical media should be sent to OPD at the following address:

Office of Orphan Products Development
Food and Drug Administration
Room 6A-55, HF-35
5600 Fishers Lane
Rockville, Maryland 20857

## IV. OTHER INFORMATION ABOUT ELECTRONIC SUBMISSIONS

### A. Electronic Format

Documents submitted in electronic format should:

- Enable the user to easily view a clear and legible copy of the information
- Include a well-structured table of contents and allow the user to navigate easily through the submission
- Enable the user to print each document page by page, as it would have been provided in paper, maintaining fonts, special orientations, table formats, and page numbers
- Allow the user to copy text, images and data electronically into other common software formats.

To achieve the above goals, all electronic documents should be submitted in text-based format if possible. References such as publications may be submitted in portable document format (PDF). PDF is an open, published format created by Adobe Systems Incorporated (http://www.adobe.com). You do not need to use a product from Adobe or from any specific company to produce your PDF documents.

### B. Scanned Documents

In general, documents scanned into text-based format are more useful for review than image-based documents. Image-based documents are more difficult to read, cannot be electronically searched, take longer to print, and occupy more storage space than text-based documents. Therefore, when possible, you should provide text-based documents, rather than image files. We understand that certain documents, such as handwritten documents and documents generated independently by your company (such as journal publications) may be available only in paper. Such paper documents can be scanned and submitted in electronic format as image-based files. However, we expect documents such as study reports recently generated by the company or recently generated as the result of the company's request to a third party to be available as text-based documents.

### C. PDF Bookmarks and Hypertext Links

Bookmarks and hypertext links are extremely important for efficient navigation through documents. For documents with a table of contents, you should provide bookmarks and hypertext links for each item listed in the table of contents including tables, figures, publications, references, and associated appendices. The bookmark hierarchy should be identical to the table of contents. Hypertext links should be included throughout the body of the document to support annotations, related sections, references, appendices, tables, or figures that are not located on the same page. It is preferable to provide the hypertext links directly to the appropriate PDF publication reference file. The link should open in a separate window and enable the user to return to the exact location in the body of the document where the link was located when it is closed.

### D. Cover Letters

A cover letter should be provided with the request. If the request is made through the FDA ESG, the cover letter will only be submitted electronically (that is, there will be no paper copy), will be located inside the request, and would be considered archival. For submissions made directly to OPD on physical media, a signed paper copy of the electronic version should be submitted with the accompanying the CD-ROMs. All cover letters should include the following:

- Description of the submission including appropriate regulatory information

- Description of the electronic submission including the type and number of electronic media used (e.g., # of CD-ROMs), and the approximate size of the submission (e.g., 2 gigabytes)

- Statement that the submission is virus free with a description of the software (name, version, and company) used to check the files for viruses

- The regulatory and information technology (IT) points of contact for the application.

E. Table of Contents

The Table of Contents should contain the required information and be organized as described in the regulations, Part 316-Orphan Drugs, Subpart C-Designation of an Orphan Drug (21 CFR 316.20 *Content and format of a request for orphan-drug designation request*)(see **Table 1**), Annual Reports (Part 316.30 *Annual reports of holder of orphan-drug designation),* or Part 814-Premarket Approval of Medical Devices, Subpart H-Humanitarian Use Devices (21 CFR 814.102 *Request for designation*)(see **Table 2**).

**Table 1: Items in an Orphan-Drug Designation Request as described in 21 CFR 316.20**

| Item | Description | |
|---|---|---|
| | Table of contents (Index) | |
| 1 | Statement of orphan-drug designation request | (§316.20(b)(1)) |
| 2 | Information on sponsor's contact person or resident agent | (§316.20(b)(2)) |
| 3 | Description of rare disease or condition | (§316.20(b)(3)) |
| 4 | Description of the drug and rationale for use | (§316.20(b)(4)) |
| 5 | Clinical superiority explanation, if applicable | (§316.20(b)(5)) |
| 6 | Drug for use in an "orphan" subset, if applicable | (§316.20(b)(6)) |
| 7 | Summary of regulatory status and marketing history of the drug | (§316.20(b)(7)) |
| 8 | Prevalence of drug's target population or cost recovery, if applicable | (§316.20(b)(8)) |
| 9 | Statement of real party of interest | (§316.20(b)(9)) |
| 10 | Other, if applicable | |

**Table 2: Items in a HUD Designation Request as described in 21 CFR 814.102**

| Item | Description | |
|---|---|---|
| | Table of contents (Index) | |
| 1 | Statement of humanitarian use device designation request | (§814.102(a)(1)) |
| 2 | Information on sponsor's contact person or resident agent | (§814.102(a)(2)) |
| 3 | Description of the targeted disease or condition | (§814.102(a)(3)) |
| 4 | Description of the device and rationale for use | (§814.102(a)(4)) |
| 5 | Demonstration of the device's target population | (§814.102(a)(5)) |
| 6 | Other (e.g., regulatory summary) | |

The table of contents, hypertext links, and bookmarks in the electronic version of a submission play the same role as the index by volume, section, and page number utilized in a paper copy. The table of contents may contain multiple levels of detail, that is, tables of subcontents. The first level of detail simply lists the items in the designation request. The second level of detail provides additional information regarding the contents for each item. Bookmarks and hyperlinks for each document or dataset should be listed for and linked to the appropriate file.

The following is an example of a portion of a Table of Contents for an orphan-drug designation request using some of the headings describing required information under 21 CFR 316.20. A Table of Contents for a HUD designation request would be similar and include headings describing required information under 21 CFR 814.102.

1. STATEMENT OF THE ORPHAN-DRUG DESIGNATION REQUEST
2. GENERAL INFORMATION
    - 3.1 Sponsor contact information
    - 3.2 Primary contact
    - 3.3 Manufacturer of the drug
3. DESCRIPTION OF THE RARE DISEASE OR CONDITION / PROPOSED INDICATION
    - 3.1 Details of the condition
        - 3.1.1. Diagnosis and screening
        - 3.1.2. Treatment
        - 3.1.3. Reasons why treatment is needed
    - 3.2 Proposed indication
4. DESCRIPTION OF THE DRUG / SCIENTIFIC RATIONALE FOR USE
    - 4.1 Description of the drug
    - 4.2 Mode of Action
    - 4.3 Rationale for use in proposed indication
5. REGULATORY SUMMARY
6. PREVALENCE OF TARGET POPULATION

F. Submission of amendments, annual reports, and correspondence

The electronic submissions of amendments, annual reports, and correspondence relating to documents previously submitted to OPD should be submitted under the original designation reference number (e.g., D061234 for an orphan-drug designation request; e.g., H061234 for a HUD designation request).

If appropriate, cover letters and tables of contents should be submitted and above guidelines should be followed with regard to format, scanning, bookmarks, and hypertext links.