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Guidance for Industry

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Providing Regulatory Submissions in

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Electronic Format —

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Orphan-Drug and

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Humanitarian Use Device Designation

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Requests and Related Submissions

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DRAFT GUIDANCE

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14 **This guidance document is being distributed for comment purposes only.**

15

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

22

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

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

37 **Guidance for Industry**
38
39 **Providing Regulatory Submissions in**
40 **Electronic Format —**
41 **Orphan-Drug and**
42 **Humanitarian Use Device Designation**
43 **Requests and Related Submissions**
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47

48 *Additional copies are available at:*

49 <http://www.fda.gov/orphan/esub/esub.htm>
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69 **U.S. Department of Health and Human Services**
70 **Food and Drug Administration**
71 **Office of Orphan Products Development (OPD)**
72 **February 2006**
73 **Electronic Submissions**

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95 **Guidance for Industry**
96 **Providing Regulatory Submissions in Electronic Format —**
97 **Orphan-Drug and Humanitarian Use Device Designation**
98 **Requests and Related Submissions**
99
100

101 This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It
102 does not create or confer any rights for or on any person and does not operate to bind FDA or the public.
103 An alternative approach may be used if such approach satisfies the requirements of the applicable statutes
104 and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for
105 implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate
106 number listed on the title page of this guidance.
107
108

109
110
111 **I. INTRODUCTION**
112

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

119
120 The goals of this guidance are to enhance the receipt, processing, review, and archiving of
121 electronic submissions to OPD.
122

123 In October 2003, the Food and Drug Administration (FDA) issued the draft guidance for industry
124 *Providing Regulatory Submissions in Electronic Format — General Considerations*. The
125 *General Considerations Guidance* discusses issues common to all types of electronic regulatory
126 submissions, such as acceptable file formats, physical media and submission procedures.¹ As set
127 forth under Part 11, Title 21, Code of Federal Regulations, for records submitted to the FDA,
128 sponsors may elect to use electronic records in lieu of paper records, in whole or part, provided
129 the requirements of Part 11 are met and the documents or parts of documents to be submitted
130 have been identified by the FDA in public docket No. 92S-0251
131 (<http://www.fda.gov/ohrms/dockets/dockets/92s0251/92s0251.htm>) as being the type of
132 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>)

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

138
139 A. Scope

140
141 This guidance applies to orphan-drug and humanitarian use device (HUD) designation requests
142 to OPD as well as related submissions such as amendments, correspondence, and annual reports.

143
144 B. Electronic Submissions

145
146 There are two ways you can provide electronic submissions to OPD. The first and preferred way
147 is completely electronic through the FDA Electronic Submissions Gateway. Alternatively, you
148 may send the submission directly to OPD on physical media with a signed paper cover letter.

149
150 We believe it is most beneficial to begin your electronic submissions with the initial submission
151 of a request for an orphan drug or HUD designation. However, if you wish to make electronic
152 submissions to previously submitted requests, please contact OPD first. You should avoid the
153 submission of any paper documents when you follow the recommendations in this document
154 except for the signed cover letter that accompanies submissions of physical media directly to
155 OPD. You should submit the electronic information for all files following the specifications
156 associated with this guidance.

157
158 Once you begin to submit a specific request in electronic format based on this guidance,
159 subsequent submissions to the request should continue to be submitted electronically.

160
161 C. Document Information for Previous Submissions

162
163 If you have submitted a request for designation in paper form and decide to submit subsequent
164 related requests (e.g., amendments, correspondence, annual reports) in electronic format based
165 on this guidance, we do not expect you to provide electronic files for the previous submissions to
166 the request. For example, if you submitted an original request in 2001 and now submit an
167 amendment to the request electronically, we do not expect you to electronically re-submit the
168 document information for the files submitted in 2001.

169
170 **II. ELECTRONIC SUBMISSIONS USING THE FDA GATEWAY (ESG)**

171
172 A. General Issues

173
174 The Food and Drug Administration (FDA) Electronic Submissions Gateway is an Agency-wide
175 solution for accepting electronic regulatory submissions. The FDA ESG enables the secure
176 submission of regulatory information for review. The FDA ESG will enable the FDA to process
177 regulatory information automatically while it functions as:

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

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

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

190
191 B. FDA ESG Preparation, Registration and Policy

192
193 There are a number of preparatory activities that should be completed before beginning the
194 registration process. There are also system hardware and software considerations to ensure
195 compatibility with and security for users of the FDA ESG. Access the internet webpage
196 <http://www.fda.gov/esg/> for all the information on FDA electronic submission gateway
197 preparation, registration, and policies. Questions regarding the process can be directed to:
198 esgprep@fda.gov.

199
200 Once registration has been completed and a digital certificate has been issued to serve as an
201 electronic signature for the sponsor, submissions to OPD through the ESG should follow the
202 format outlined in Part IV. OTHER INFORMATION ABOUT ELECTRONIC SUBMISSIONS.
203 Questions regarding the format of electronic submissions should be directed to the electronic
204 submission coordinator for orphan-drug designation requests at desigesub@fda.hhs.gov or for
205 HUD designation requests at hudesub@fda.hhs.gov .

206
207 **III. ELECTRONIC SUBMISSIONS USING PHYSICAL MEDIA (E.G. CD-ROMS)**

208
209 A second option for the electronic submission of documents to FDA is via physical media sent
210 directly to OPD. This option is completely separate from the ESG.

211
212 Physical media should be submitted 1) as described in the *General Considerations Guidance*
213 (<http://www.fda.gov/cder/guidance/4156dft.pdf>); 2) protected (e.g., in a sleeve, jewel case,
214 physical media mailer); and 3) be attached securely to a jacket (e.g., notebook, binder).

215
216 The jacket should include a signed paper copy of the cover letter for the submission and the
217 electronic media for archiving. Note in the cover letter that the submission is in electronic
218 format and is virus free with a description of the software (name, version, and company) used to
219 check the files for viruses.

220
221 Each unit of physical media and its jacket should be labeled with the following:

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- 222
- 223
- 224
- 225
- 226
- 227
- 228
- 229
- 230
- 231
- 232
- 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)

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

237

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

241

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

243

244 Office of Orphan Products Development
245 Food and Drug Administration
246 Room 6A-55, HF-35
247 5600 Fishers Lane
248 Rockville, Maryland 20857

249

250 **IV. OTHER INFORMATION ABOUT ELECTRONIC SUBMISSIONS**

251

252 A. Electronic Format

253

254 Documents submitted in electronic format should:

- 255
- 256
- 257
- 258
- 259
- 260
- 261
- 262
- 263
- 264
- 265
- 266
- 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.

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

272
273 B. Scanned Documents

274
275 In general, documents scanned into text-based format are more useful for review than image-
276 based documents. Image-based documents are more difficult to read, cannot be electronically
277 searched, take longer to print, and occupy more storage space than text-based documents.
278 Therefore, when possible, you should provide text-based documents, rather than image files. We
279 understand that certain documents, such as handwritten documents and documents generated
280 independently by your company (such as journal publications) may be available only in paper.
281 Such paper documents can be scanned and submitted in electronic format as image-based files.
282 However, we expect documents such as study reports recently generated by the company or
283 recently generated as the result of the company's request to a third party to be available as text-
284 based documents.

285
286 C. PDF Bookmarks and Hypertext Links

287
288 Bookmarks and hypertext links are extremely important for efficient navigation through
289 documents. For documents with a table of contents, you should provide bookmarks and
290 hypertext links for each item listed in the table of contents including tables, figures, publications,
291 references, and associated appendices. The bookmark hierarchy should be identical to the table
292 of contents. Hypertext links should be included throughout the body of the document to support
293 annotations, related sections, references, appendices, tables, or figures that are not located on the
294 same page. It is preferable to provide the hypertext links directly to the appropriate PDF
295 publication reference file. The link should open in a separate window and enable the user to
296 return to the exact location in the body of the document where the link was located when it is
297 closed.

298 D. Cover Letters

299
300 A cover letter should be provided with the request. If the request is made through the FDA ESG,
301 the cover letter will only be submitted electronically (that is, there will be no paper copy), will be
302 located inside the request, and would be considered archival. For submissions made directly to
303 OPD on physical media, a signed paper copy of the electronic version should be submitted with
304 the accompanying the CD-ROMs. All cover letters should include the following:

- 305
306
- 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)
- 307
308
309
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311

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- 312 • Statement that the submission is virus free with a description of the software (name,
313 version, and company) used to check the files for viruses
314
- 315 • The regulatory and information technology (IT) points of contact for the application.
316

317 E. Table of Contents
318

319 The Table of Contents should contain the required information and be organized as described in
320 the regulations, Part 316-Orphan Drugs, Subpart C-Designation of an Orphan Drug (21 CFR
321 316.20 *Content and format of a request for orphan-drug designation request*)(see **Table 1**),
322 Annual Reports (Part 316.30 *Annual reports of holder of orphan-drug designation*), or Part 814-
323 Premarket Approval of Medical Devices, Subpart H-Humanitarian Use Devices (21 CFR
324 814.102 *Request for designation*)(see **Table 2**).
325

326 **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

327

328 **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)

329

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

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

- 340
- 341 1. STATEMENT OF THE ORPHAN-DRUG DESIGNATION REQUEST
 - 342 2. GENERAL INFORMATION
 - 343 3.1 Sponsor contact information
 - 344 3.2 Primary contact
 - 345 3.3 Manufacturer of the drug
 - 346 3. DESCRIPTION OF THE RARE DISEASE OR CONDITION / PROPOSED INDICATION
 - 347 3.1 Details of the condition
 - 348 3.1.1. Diagnosis and screening
 - 349 3.1.2. Treatment
 - 350 3.1.3. Reasons why treatment is needed
 - 351 3.2 Proposed indication
 - 352 4. DESCRIPTION OF THE DRUG / SCIENTIFIC RATIONALE FOR USE
 - 353 4.1 Description of the drug
 - 354 4.2 Mode of Action
 - 355 4.3 Rationale for use in proposed indication
 - 356 5. REGULATORY SUMMARY
 - 357 6. PREVALENCE OF TARGET POPULATION
- 358
- 359 F. Submission of amendments, annual reports, and correspondence
- 360

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

365

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