Guidance for Industry
Providing Regulatory Submissions in Electronic Format — General Considerations

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.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be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance.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*.

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Food and Drug Administration
Center for Biologic Evaluation and Research (CBER)
Center for Drug Evaluation and Research (CDER)
Center for Devices and Radiological Health (CDRH)
Center for Food Safety and Applied Nutrition (CFSAN)
Center for Veterinary Medicine (CVM)

October 2003
Electronic Submissions
Revision 1

Guidance for Industry

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Additional copies are available at:

http://www.fda.gov/cder/guidance/index.htm
or
http://www.fda.gov/cber/guidelines.htm
or
http://www.fda.gov/cvm/guidance/guidance.html
or
http://www.cfsan.fda.gov/~dms/guidance.html

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2 ## Providing Regulatory Submissions in Electronic Format –
3 ## General Considerations
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5

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15
16
17 ## I.   INTRODUCTION
18
19 This is one in a series of guidance documents intended to assist you when making regulatory
20 submissions in electronic format to the Food and Drug Administration (FDA). This guidance
21 discusses general issues common to all types of electronic regulatory submissions. This is a
22 revision to the guidance of the same name that issued in January 1999. Once it has been
23 finalized, this guidance will replace the January 1999 guidance.
24
25 This guidance is being revised to address electronic submissions coming into **all** centers of the
26 Agency. Changes from the 1999 version of the guidance also include addition of a new section
27 describing the relationship of electronic submissions to 21 CFR part 11. There are updates on the
28 recommendations for creating PDF documents including specific guidance for the use of fonts.
29 New file formats for data, specifically XML and SGML are introduced. The electronic
30 transmission of files is discussed. In some cases, the guidance for one center differs some from
31 that of another center because of differences in procedures and in the computer infrastructures in
32 the centers. We will work to minimize these differences wherever possible.
33
34 Agency guidance documents on electronic regulatory submissions will be updated regularly to
35 reflect the evolving nature of the technology involved and the experience of those using this
36 technology.
37
38 FDA's guidance documents, including this guidance, do not establish legally enforceable
39 responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should
40 be viewed only as recommendations, unless specific regulatory or statutory requirements are

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[1] This guidance has been prepared by the Center for Drug Evaluation and Research (CDER) in cooperation with the
Center for Biologics Evaluation and Research (CBER), Center for Devices and Radiological Health (CDRH), Center
for Food Safety and Applied Nutrition (CFSAN), and Center for Veterinary Medicine (CVM) at the Food and Drug
Administration.

41 cited. The use of the word *should* in Agency guidances means that something is suggested or
42 recommended, but not required.
43
44
45 **II.   BACKGROUND**
46
47 In the *Federal Register* of March 20, 1997 (62 FR 13430), the FDA published the Electronic
48 Records; Electronic Signatures regulation (21 CFR part 11). This regulation provides, among
49 other things, for the voluntary submission of parts or all of records in electronic format without
50 an accompanying paper copy under certain circumstances. In January 1999, the Center for
51 Biologics Evaluation and Research (CBER) and the Center for Drug Evaluation and Research
52 (CDER) finalized a joint guidance document on general considerations for electronic
53 submissions. They also published guidance documents describing how to provide marketing
54 applications to each center. Following publication of these guidance documents, a working
55 group was formed with the CBER, CDER, Center for Devices and Radiological Health (CDRH),
56 the Center for Food Safety and Applied Nutrition (CFSAN), and the Center for Veterinary
57 Medicine (CVM) to coordinate electronic submission activity. The efforts of this working group
58 have resulted in this draft guidance, which updates the 1999 general considerations guidance
59 document.
60
61 The Agency envisions a series of guidance documents on electronic regulatory submissions. As
62 individual documents are completed, they will be issued first in draft for comment, then finalized
63 and added to the series. The guidances will be updated regularly to reflect the continuously
64 evolving nature of the technology and experience of those using this technology.
65
66
67 **III.   HOW DO ELECTRONIC SUBMISSIONS RELATE TO 21 CFR PART 11?**
68
69 FDA's part 11 regulations (21 CFR part 11), among other things, set forth the criteria under
70 which records submitted to FDA may be submitted in electronic format in place of paper.
71 Section 11.2(b) states that, for records submitted to the Agency, persons may use electronic
72 records in lieu of paper records, in whole or part, provided the requirements of part 11 are met
73 and the documents or parts of documents to be submitted have been identified by the Agency in
74 public docket No. 92S-0251 as being the type of submission the Agency is prepared to accept in
75 electronic format.[2]
76
77
78 **IV.   WHAT FILE FORMATS SHOULD I USE FOR ELECTRONIC DOCUMENTS?**
79
80 Documents submitted in electronic format should:
81
82   •   Enable the user to easily view a clear and legible copy of the information
83

---

[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.

84   •   Enable the user to print each document page by page, as it would have been
85   provided in paper, maintaining fonts, special orientations, table formats, and page
86   numbers
87
88   •   Include a well-structured table of contents and allow the user to navigate easily
89   through the submission
90
91   •   Allow the user to copy text, images and data electronically into other common
92   software formats.
93
94 To achieve the above goals, you should submit all electronic documents in portable document
95 format (PDF). We are prepared to archive documents provided as PDF files. PDF is an open,
96 published format created by Adobe Systems Incorporated (http://www.adobe.com). You do not
97 need to use a product from Adobe or from any specific company to produce your PDF
98 documents. PDF has been accepted as a standard for providing documents in electronic format
99 by the International Conference on Harmonisation (ICH).
100
101 The following will help you create PDF files that we can review and archive.
102
103   **A.**   **Version**
104
105   We should be able to read all PDF files with Acrobat Reader version 4.0, and above, with
106   the search plug in. We should not need any additional software to read and navigate the
107   PDF files.
108
109   **B.**   **Fonts**
110
111   PDF viewing software automatically substitutes a font to display text if the font used to
112   create the text is unavailable on the reviewer's computer. In some cases, font substitution
113   can occur even when the fonts are available. For example, Helvetica or Times are
114   substituted even if available on the reviewer's computer. Font substitution can affect a
115   document's appearance and structure, and in some cases it can affect the information
116   conveyed by a document. We cannot guarantee the availability of any one font.
117   Therefore, you should embed all fonts you are using in the PDF files to ensure that those
118   fonts will always be available to the reviewer. When embedding fonts, all characters for
119   the font should be embedded, not just a subset of the fonts being used in the document.
120
121   However, font embedding does not solve the problems that occur when a reviewer tries to
122   paste text from a PDF document into another software format. If the font is not available
123   on the reviewer's computer, font substitution results even if the fonts are embedded. For
124   this reason, we ask that you restrict the fonts used in documents to one of the following
125   fonts listed in Table 1. We still ask that you embed the fonts so they are available for
126   printing older archival files.
127

128   **Table 1: List of recommended fonts**

Font type	Font name
San Serif	AdobeSansMM (Adobe Sans Multiple Master)
	Arial BolitaMT (Arial Bold Italic (From Monotype))
	ArialBolMT (Arial Bold Monotype)
	ArialtaMT Arial Italic (Monotype)
	ArialMT Arial (Monotype)
Non proportional	Couri (Courier)
	CouriBol (Courier Bold)
	CourriBolObl (Courier Bold Oblique)
Serif	AdobeSerifMM (Adobe Serif Multiple Masters)
	TimesNewRomPSBolitaMT (Times New Roman Bold Italic)
	TimesNewRomPSBolMT (Times New Roman Bold)
	TimesNewRomPSItaMT (Times New Roman Italic)
	TimesNewRomPSMT (Times New Roman)
	TimesNewRoman
Other	Symbo (Symbol)
	ZapfDin (Zapf Dingbats)

129

130

131   Resizing a submitted document because the contents are too small to read is inefficient.
132   We believe that Times New Roman, 11 or 12-point font (the font used for this
133   document), is adequate in size for reading narrative text. When making point size larger,
134   data comparisons could become problematic because data that normally might appear in
135   one table would now appear in multiple tables. When choosing a point size for tables, a
136   balance should be made between providing sufficient information on a single page that
137   may facilitate data comparisons while still achieving a point size that remains legible.
138   Generally, point sizes 9-10 are recommended for tables; smaller point sizes should be
139   avoided. Ten point fonts are recommended for footnotes.

140

141   We recommend the use of a black font color. Blue font can be used for hypertext links
142   (preferred for submissions to CBER[3] and CFSAN). If a font color other than black is
143   used, you should avoid light colors that do not print well on grayscale printers. You can
144   test the color reproduction prior to submission by printing sample pages from the
145   document using a grayscale printer.

146

147   **C.   Page Orientation**

148

---

[3] The Commissioner has announced a consolidation of the CDER/CBER review functions for therapeutic products. Once the consolidation has been completed, we will review those guidances that have been affected by the transfer of functions for possible revision.

149   Pages should be properly oriented to reduce the effort of rotating pages. For example,
150   you should set the page orientation of landscape pages to landscape prior to saving the
151   PDF document in final form to ensure correct page presentation.
152
153   **D.**   **Page Size and Margins**
154
155   The print area for pages should fit on a sheet of paper that is 8.5 inches by 11 inches.
156   You should allow a margin of at least 1 inch on the left side of page (to avoid obscuring
157   information when the pages are subsequently printed and bound) and 3/8 of an inch on
158   the other sides. For pages in landscape orientation, you should allow 3/4 of an inch at the
159   top to allow more information to be displayed legibly on the page. Header and footer
160   information can appear within these margins as long as it is not within 3/8 of an inch of
161   the edge of the 8.5 by 11 inch page, because the text may be lost upon printing or being
162   bound.
163
164   **E.**   **Source of Electronic Document**
165
166   PDF documents produced by scanning paper documents are usually inferior to those
167   produced from an electronic source document. Scanned documents are more difficult to
168   read and do not allow us to search or copy and paste text for editing in other documents.
169   They should be avoided if at all possible. If you use optical character recognition
170   software, you should verify that all imaged text converted by the software is accurate.
171
172   **F.**   **Methods for Creating PDF Documents and Images**
173
174   You should choose a method for creating PDF documents that produces the best
175   replication of a paper document. You can ensure that the paper and PDF version of the
176   document are the same by printing the document from the PDF version.
177
178   Documents that are available only in paper should be scanned at resolutions that will
179   ensure the pages are legible both on the computer screen and when printed. At the same
180   time, you should also limit the file size. We recommend scanning at a resolution of 300
181   dots per inch (dpi) to balance legibility and file size. We discourage the use of grayscale
182   or color because of file size. But, if you believe their use is necessary, the following
183   paragraphs provide preliminary recommendations, and specific guidance documents
184   provide additional details. After scanning, you should avoid resampling to a lower
185   resolution.
186
187   The optimal image resolution and bit depth depends to a large part on the actual need for
188   viewing the image. You should not provide images at high resolution and depth without
189   determining the need. High resolution and depth images result in large files, taking up
190   valuable storage space. It is better to provide samples to the appropriate center of the
191   images at various resolutions and depths prior to sending in the actual submissions to
192   determine the optimal image resolution and depth to meet the review need.
193

194 When creating PDF files containing images, you should not resample images.
195 Resampling does not preserve all of the pixels in the original. For PDF images, you can
196 use one of the following lossless compression techniques.
197
198 •   For lossless compression of color and grayscale images, you should use Zip/Flate
199   (one technique with two names). This is specified in Internet RFC 1950 and RFC
200   1951 (http://info.internet.isi.edu/in-notes/rfc/files/rfc1950.txt).
201
202 •   For lossless compression of black and white images, you should use the CCITT
203   Group 4 Faxcompression technique. It is specified as CCITT recommendations
204   T.6 (1988) - *Facsimile coding schemes and coding control functions for Group 4*
205   *facsimile apparatus*.
206
207 When submitting medical images to CBER, such as X-ray, CT, ultra sound, PET, and
208 SPECT, they should not be compressed.
209
210 *Note: if you use lossless compression, there should not be a change in the label size and*
211 *format.*
212
213 Paper documents containing handwritten notes should be scanned at 300 dpi.
214 Handwritten notes should be done in black ink for clarity.
215
216 For photographs, the image should be obtained with a resolution of 600 dpi. If black and
217 white photos are submitted, consider 8-bit gray scale images. If color photos are
218 submitted, consider 24-bit RGB images. A captured image should not be subjected to
219 nonuniform scaling (i.e., sizing).
220
221 Gels and karyotypes should be scanned directly, rather than from photographs. Scanning
222 should be at 600 dpi and 8-bit grayscale depth.
223
224 Plotter output graphics should be scanned or captured digitally at 300 dpi.
225
226 High-pressure liquid chromatography or similar images should be scanned at 300 dpi.
227
228 When color is important in the review of a file, labeling for example, you should make
229 sure that the colors are an accurate representation of the actual image. Since color varies
230 from monitor to monitor, it is difficult to ensure that the reviewer will see exactly the
231 same color as in the actual image. However, for printing, there is more control over the
232 color if you use CMYK color model as opposed to the RGB model. Since PDF uses the
233 color profile provided by CMYK, you can use Pantone Matching and this will ensure
234 color consistency for printing. PDF also uses the ICC color profile specifications when
235 PDF documents are printed.
236
237 **G.   Hypertext Linking and Bookmarks**
238

239 Hypertext links and bookmarks are techniques used to improve navigation through PDF
240 documents. Hypertext links can be designated by rectangles using thin lines or by blue
241 text (the latter is preferred by CBER and CFSAN). We recommend you use invisible
242 rectangles for hypertext links in a table of contents to avoid obscuring text.
243 Recommendations for hypertext linking and bookmarks are provided in the guidance for
244 the specific submission type.

245

246 In general, for documents with a table of contents, you should provide bookmarks and
247 hypertext links for each item listed in the table of contents including all tables, figures,
248 publications, other references, and appendices. These bookmarks and hypertext links are
249 essential for the efficient navigation through documents. Bookmarks to the roadmap
250 (when applicable), main table of contents, and item table of contents for the section of the
251 application a reviewer has accessed, at the top of the bookmark hierarchy, are extremely
252 helpful. The bookmark hierarchy should be identical to the table of contents with
253 exceptions made for the following three bookmarks – the roadmap (when applicable), the
254 main table of contents, and the item table of contents being accessed by a reviewer. You
255 should avoid using bookmark levels in addition to those present in the table of contents.
256 Each additional level increases the need for space to read the bookmarks. We
257 recommend using no more than 4 levels in the hierarchy.

258

259 Hypertext links throughout the body of the document to supporting annotations, related
260 sections, references, appendices, tables, or figures that are not located on the same page
261 are helpful and these hypertext links improve navigation efficiency. You should use
262 relative paths when creating hypertext linking to minimize the loss of hyperlink
263 functionality when folders are moved between disk drives. Absolute links that reference
264 specific drives and root directories will no longer work once the submission is loaded
265 onto our network servers.

266

267 When creating bookmarks and hyperlinks, you should choose the magnification setting
268 *Inherit Zoom* so that the destination page displays at the same magnification level that the
269 reviewer is using for the rest of the document.

270

271 **H. Page Numbering**

272

273 See guidance for the specific submission type for guidance on page numbering.

274

275 In general, it is easier to navigate through an electronic document if the page numbers for
276 the document and the PDF file are the same. The initial page of the document should be
277 numbered as page one, with two exceptions. One, when a document is split because of
278 its size (e.g., > 50 MB), the second or subsequent file should be numbered consecutively
279 to that of the first or preceding file. Two, when several small documents with their own
280 internal page numberings have been brought together into a single file, it is not necessary
281 to renumber the documents into one page sequence, although you should provide a
282 bookmark at the start of each subdocument. For example, if you are adding an original
283 protocol as an appendix to a study report, you should not add page numbers to the

284   original protocol so the page numbers are consecutive to the rest of the study report. You
285   should provide a bookmark to the original protocol.
286
287   **I.   Document Information Fields**
288
289   Document information fields are used to search for individual documents and to identify
290   the document when found. Recommendations for the document information fields will
291   be provided in the guidance for the specific submission type.
292
293   **J.   Open Dialog Box**
294
295   The open dialog box sets the document view when the file is opened. The initial view of
296   the PDF files should be set as *Bookmarks* and *Page*. If there are no bookmarks, we
297   recommend that you set the initial view as *Page* only. You should set the *Magnification*
298   and *Page Layout* to default.
299
300   **K.   Naming PDF Files**
301
302   Recommendations on names to use for folders and selected files are provided in the
303   individual guidances for specific submission types. For uniformity, you should use our
304   specific naming conventions when they are provided. Reviewers are trained to look for
305   these folders and files, and using the recommended names should help avoid
306   misunderstandings, improve communication, and speed the review of a submission.
307
308   When we do not specify a file name, you can use file names up to 32 characters in length
309   including PDF as the 3-character extension. We recommend that you avoid using
310   punctuation, dashes, spaces, or other nonalphanumeric symbols (e.g., \ / : * ? < > | " % #
311   +) in file names. Underlines can be used.
312
313   **L.   Security**
314
315   You should not include any security settings or password protection for PDF files except
316   when recommended in guidance for a specific submission type. You should allow
317   printing, changes to the document, selecting text and graphics, and adding or changing
318   notes and form fields. Our internal security and archival processes will maintain the
319   integrity of the submitted files. A read-only copy of the files, generated from the
320   submitted files, will be provided to the reviewer.
321
322   **M.   Indexing PDF Documents**
323
324   We use full text indexes to help find specific documents and/or search for text within
325   documents. When a document or group of documents is indexed, all words and numbers
326   in the file and all information stored in the document information fields are stored in
327   special index files that are functionally accessible using the search tools available in
328   Acrobat. Portions of a document that are imaged are not indexed. Even if the document

329   only contains images, the text in the Document Information fields of the file will be
330   indexed.
331
332   These full text indexes should not be confused with a table of contents. Adobe Acrobat
333   Catalog is one example of a tool that can be used to index PDF documents. Indexes
334   should not require extensions or additions to the off-the-shelf Acrobat Reader.
335
336   With many submissions, we ask that you associate the table of contents file for a section
337   with the corresponding full text index file. By *associate*, we mean that when the table of
338   contents file is opened, the index file is automatically added to the available index list and
339   is ready to be used.
340
341   Further recommendations for full text indexes will be provided in individual guidances
342   for the specific submission types.
343
344   **N.   Plug Ins**
345
346   You can use plug ins to assist in the creation of a submission. However, the review of the
347   submission should not require the use of any plug ins, in addition to those provided with
348   the latest Acrobat Reader because we are not prepared to archive additional plug-in
349   functionality.
350
351
352 **V.   WHAT FILE FORMATS SHOULD I USE FOR ELECTRONIC DATASETS?**
353
354 You should provide data subsets in certain formats. Currently, we are able to accept and archive
355 datasets in SAS System XPORT transport format (Version 5 SAS transport file). In
356 circumstances when data are moved directly to a database or special review tool, tagged ASCII
357 file, specifically, standard generalized markup language (SGML) and extensible markup
358 language (XML), may be the appropriate file format. At times, delimited ASCII files are also
359 acceptable. See the individual guidance for the specific submission type for the appropriate
360 dataset format.
361
362   **A.   SAS System XPORT Transport Format (Version 5 SAS Transport Format)**
363
364   SAS XPORT transport format, also called Version 5 SAS transport format, is an open
365   format published by the SAS Institute. The description of this SAS transport file format is
366   in the public domain. Data can be translated to and from this SAS transport format to
367   other commonly used formats without the use of programs from SAS Institute or any
368   specific vendor.
369
370   You should follow the recommendations in this section to create SAS transport files that
371   we can review and archive.
372

373   *1.   Version*
374
375   In SAS, SAS XPORT transport files are created by PROC XCOPY in Version 5
376   of SAS software and by the XPORT engine in Version 6 and higher of SAS
377   Software. We are unable to archive SAS Transport files processed by the CPORT
378   engine.
379
380   You can find the record layout for SAS XPORT transport files in SAS technical
381   support TS-140. This document and additional information about the SAS
382   Transport file layout can be found on the SAS World Wide Web page at
383   http://www.sas.com/fda-esub.
384
385   *2.   Transformation of Datasets*
386
387   We use a variety of software tools to analyze the datasets. Stat/Transfer from
388   Circle Systems and DBMS/copy from Conceptual Software Inc., are two
389   programs used to convert data to various formats used for analysis. SAS Viewer
390   version 7 or higher is used to open SAS transport files directly.
391
392   *3.   Naming SAS Transport Files*
393
394   All SAS transport files should use *xpt* as the file extension.
395
396   *4.   Compression of SAS Transport Files*
397
398   SAS transport files should not be compressed. There should be one transport file
399   per dataset.
400
401   *5.   Content of Datasets and Organization*
402
403   You should provide a single transport file for each dataset. Many of the software
404   tools used by the reviewers require datasets to be loaded into random access
405   memory (RAM) prior to opening the file. Therefore, dataset files should be
406   organized so that their size is generally less than 50 MB per file. Datasets divided
407   to meet the maximum size restrictions should contain the same variable
408   presentation so they can be easily merged, joined, and concatenated. The datasets
409   should be accompanied by data definition tables that include metadata such as the
410   variable name, a description of the variable, the type of variable (e.g., number,
411   character, date), and codes used in the dataset. Variable names should be limited
412   to 8 characters. You should include a descriptive name up to 40 characters in the
413   label header. Further recommendations for content of SAS Transport files are
414   provided in guidance for each specific submission type.
415
416   We recommend that you discuss the content of the datasets with the review
417   division prior to submission.

418
419   **B.   XML**
420
421   Extensible markup language (XML) was developed by a working group at the World
422   Wide Web Consortium (W3C). It is a nonproprietary language developed to improve on
423   previous mark up languages including standard generalized markup language (SGML)
424   and hypertext markup language (HTML). XML is not as complicated to use as SGML
425   and is more flexible than HTML.
426
427   Information in an XML file is divided into specific pieces. These pieces are called objects
428   or elements types. The element type identifies the piece of information. For example, the
429   NDA application number might be identified with the element type <appNum>. All
430   element type names are bracketed using the special characters < >. Inside the XML
431   document, the element type name is placed just prior to the piece of information and after
432   the information. This is called tagging. So, in the XML file, the application number for
433   NDA 123456 would be tagged as follows <appNum>123456</appNum>. The / prior to
434   the element type denotes that this is the end of the information about the appNum.
435
436   By using a hierarchial structure, XML allows you to relate two or more elements. This is
437   accomplished by nesting one element within another.
438
439   Additional information about the element type is provided by attributes. Attributes are
440   placed within the element types and are surrounded by " ". For example, if you wanted
441   to identify the type of the application number as an NDA, you could add this piece of
442   information as an attribute. This could be represented in the XML file as <appNum
443   type="NDA">123456</appNum>.
444
445   Internet browsers read XML files. Style sheets provide the browser with the information
446   necessary to create tables, fonts, and colors for display in the XML file.
447
448   The specific names of the element types and attributes as well as the valid syntax,
449   structure and format for defining the XML elements are included in a file called
450   document type declaration (DTD). If the XML document does not follow the DTD, the
451   file might not be used properly.
452
453   We currently use XML version 1.0 recommended by the World Wide Web Consortium
454   (W3C). We will be evaluating additional uses for XML as enhancements for data
455   exchange evolve and extensions are developed. Additional information can be found at
456   the W3C web site at www.w3c.org.
457
458   For specific tags and formats see the individual guidance document for the specific
459   submission type.
460
461   **C.   SGML**
462

463   A working group at the W3C developed standard generalized markup language (SGML).
464   It is a nonproprietary language developed to organize and transmit information in digital
465   format. It shares many of the features of XML described above. Additional information
466   can be found at the W3C web site at www.w3c.org.
467
468   **D.   Molfiles**
469
470   The file format called *Molfile* is in the public domain and was developed by Molecular
471   Design Limited (MDL) in the late 1970's. Currently, the company, now named
472   Molecular Design Limited Information Systems, is a wholly owned subsidiary of Elsevier
473   Science. Technical information about the Molfile format can be found at the MDL web
474   site at http://www.mdli.com/downloads/literature/ctfile.pdf.
475
476   Molfiles are generated by chemical structure drawing programs. The most common
477   drawing programs, ISIS/Draw from MDL and ChemDraw Pro from Cambridge Soft
478   (http://www.cambridgesoft.com), create Molfiles. A free copy of ISIS/DRAW for your
479   personal use may be obtained from the MDL Web site at
480   http://www.mdli.com/downloads/isisdraw.html.
481
482   Molfiles can be viewed and reformatted using Chime, a free plug in to Microsoft
483   Internet Explorer and Netscape Communicator from MDL. You can download the plug
484   in at http://www.mdli.com/downloads/chime.html.
485
486   Molfiles can be searched using database programs such as ISIS Base. Additional
487   Information about this database program can be found at the MDL web site at
488   http://www.mdli.com.
489
490
491 **VI.   WHAT ARE THE PROCEDURES FOR SENDING ELECTRONIC**
492 **SUBMISSIONS FOR ARCHIVE?**
493
494 Electronic submissions should be provided in electronic format, either on physical media or by
495 acceptable methods of electronic transport. You should refer to the individual guidance for the
496 specific submission type for the appropriate procedures to use for sending electronic submissions
497 for archive.
498
499   **A.   Electronic Transmission**
500
501   Currently, we have identified three methods for sending submissions electronically.
502   Submissions using electronic data interchange (EDI), web-based transmissions, and
503   secure email. We will provide additional information on these transmission methods as
504   they are used for specific submission types. For example, CVM accepts electronic
505   submission of certain types by attaching encrypted PDF files to e-mail to the Electronic
506   Document Control Unit at cvmdcu@cvm.fda.gov. You can get more information at
507   www.fda.gov/cvm/fda/TOCs/guideline.html.

508
509 **B.   Physical Media**
510
511 The following information is important when sending electronic submissions on physical
512 media. See Appendix A: Additional information on providing Electronic Submissions
513 on Physical Media for additional information.
514
515 *1.   Where do I send the electronic submission?*
516
517 Electronic submissions should be sent directly to the appropriate center involved. See
518 guidance for specific submission type for additional information.
519
520 • CBER
521
522 You should provide a minimum of two copies of the submission. One copy will be
523 used to load the submission into our electronic document room (EDR). This copy
524 will be made available to the Agency's review community upon request. The second
525 copy will be archived for disaster recovery. Additional copies of items of an
526 application, bundled by review discipline, may be requested to facilitate the review
527 offsite. All materials are received centrally within CBER and should be addressed as
528 follows:
529
530   Center for Biologics Evaluation and Research
531   Document Control Center, HFM-99
532   Food and Drug Administration
533   1401 Rockville Pike
534   Rockville, MD 20852-1448
535
536 Submitting organizations should use the above address for regulatory documents and
537 media in support of applications within CBER. This includes regulatory documents and
538 media sent via U.S. Postal Service or via common or private carriers.
539
540 • CDER
541
542 Unless otherwise specified in the specific submission guidance, send one copy of the
543 electronic regulatory submission for archive to the CDER Central Document Room.
544
545 • CDRH
546
547 Contact the appropriate reviewing division prior to making an electronic submission.
548 The division will inform you as to where and how to send submissions. Contacts can be
549 found at http://www.fda.gov/cdrh/organize.html#ODE. See individual guidance for
550 specific submission type for additional information.

551
552   • CFSAN

553

554   CFSAN's Office of Nutritional Products, Labeling, and Dietary Supplements (ONPLDS)
555   is working on procedures for submitting new dietary ingredient notifications and
556   applications for temporary marketing permits. Unless otherwise specified in the specific
557   submission guidance, send one copy of the electronic regulatory submission for ONPLDS
558   to the following address:

559

560   Office of Nutritional Products, Labeling, and Dietary Supplements
561   Center for Food Safety and Applied Nutrition
562   5100 Paint Branch Parkway, HFS-800
563   College Park, MD 20740

564

565

566   Currently, CFSAN's Office of Food Additive Safety (OFAS) accepts a submission
567   provided only on physical media. All submissions should be sent directly to OFAS. The
568   procedure for handling paper submissions is unchanged from the past.

569

570   You should send electronic and paper submissions to:

571

572   Office of Food Additive Safety
573   Center for Food Safety and Applied Nutrition
574   Food and Drug Administration
575   5100 Paint Branch Parkway
576   College Park, MD 20740

577

578   You should communicate with OFAS prior to submitting an electronic document,
579   notifying it of your intention to submit an electronic document in advance of the target
580   date for the submission

581

582   OFAS will schedule a teleconference or meeting between petitioners and the appropriate
583   OFAS staff. The objective of the teleconference is to convey information relating to the
584   proposed electronic submission's management paradigm, content, format, and structure.
585   Moreover, OFAS will discuss any issues specific to your submission that may not have
586   been fully addressed in this general considerations guidance. The amount of time that
587   will be needed to ensure that the document is ready for submission will depend on the
588   complexity of the document and experience of the said submitter in preparing petitions
589   and notifications.

590

591   • CVM

592

593   We are working on procedures for accepting electronic submissions on physical media.
594   See individual guidance for specific submission type for additional information.

595

596   *2.   What type of media should I use?*
597

598   We are prepared to accept electronic submissions on CD-ROM and digital tape. In
599   CDER and CFSAN, you can also use floppy disks. To optimize processing efficiency,
600   we recommend choosing media with a capacity most appropriate to the size of the
601   submission. Whenever possible, applicants should choose media capable of holding the
602   submission on the *fewest* number of units.
603

Recommendations for Media		
Size of Submission	**Media and format**	**Units**
Less than 10MB*	3.5 inch DOS Formatted Floppy Disks	1 to 10
Less than 3.25GB	CD-ROM ISO 9660	1 to 5 CDs
Greater than 3.25GB	Digital Linear Tape (DLT) 35/70, 20/40 and 10/20 GB format using NT server 4.0 with NT backup or backup exec.	No limit

604   *This is not an option for CBER and CVM
605

606   *3.   How should I prepare the media for electronic submissions?*
607

608   You should send all electronic media adequately secured in a standard binder marked
609   clearly on the outside ELECTRONIC REGULATORY SUBMISSION FOR ARCHIVE.
610   CDs should be packaged carefully to ensure that they arrive in a usable condition.
611   Particularly vulnerable are diskettes and CD jewel cases shipped in envelopes without
612   bubble-type protective material or stiff backing. We do not recommend the use of jiffy-
613   type bags alone to ship media because they may not provide adequate protection.
614

615   You should provide the following identification information on the media, as appropriate:
616

617   •   Sponsor, applicant or company name
618   •   Name of the product, chemical, or ingredient
619   •   Appropriate regulatory ID number (e.g., Petition Notification number, NDA,
620   IND, BLA number, petition or notification number)
621   •   Application type (e.g., IND amendment, BLA supplement, title of petition or
622   notification)
623   •   Submission date in the format of dd-mmm-yyyy
624   •   Copy number (e.g., original, copy 1, copy 2)
625   •   Media series (e.g., "1 of 1," "1 of 2")
626   •   When sending CD-ROMs to OFAS, number them from 0.001 through 0.XXX
627   for the original submission, and 1.001 through 1.XXX for subsequent
628   submissions to the same files with additional information.
629
630

631   You should include the information directly on the DLT tape cover label. For CDROMs,
632   you should include the information on the jewel case. The CDROM itself should include,

633   at a minimum, sufficient identification information so that it can be paired with the jewel
634   case bearing the complete identification information, in the event that they become
635   separated. See the individual guidance for the specific submission type for additional
636   information on labeling physical media.
637
638

639   **VII.   WHAT IF I HAVE A QUESTION?**
640

641   **A.   CBER**
642

643   You can submit questions pertaining to the preparation of submissions, in electronic
644   format, for CBER to ESUBPREP@CBER.fda.gov.
645

646   **B.   CDER**
647

648   We maintain a web site on electronic submissions at
649   www.fda.gov/cder/regulatory/ersr/default.htm. You can direct questions regarding the
650   preparation of submissions in electronic format in CDER to esub@cder.fda.gov.
651

652   **C.   CDRH**
653

654   You can submit questions about electronic submissions via email to esub@cdrh.fda.gov.
655   We also maintain a web site on electronic submissions at
656   www.fda.gov/cdrh/elecsub.html. In addition, you can sign up for email updates on the
657   CDRH home page at www.fda.gov/cdrh.
658

659   **D.   CFSAN**
660

661   You can direct questions regarding the preparation of submissions in electronic format in
662   CFSAN to the Electronic Submissions Coordinator email esubprep@opa.fda.gov.
663

664   **E.   CVM**
665

666   You can direct questions regarding the preparation of submissions in electronic format in
667   CVM to the Electronic Submissions Coordinator, email cvmstars@cvm.fda.gov or you
668   can call the Center Hot Line at 301-827-8277. Additional information on electronic
669   submissions can be found at http://www.fda.gov/cvm/guidance/guidance.html.
670
671

672
673 **APPENDIX A: ADDITIONAL INFORMATION ON PROVIDING ELECTRONIC**
674 **SUBMISSIONS ON PHYSICAL MEDIA**
675
676 **CBER**
677
678 *Processing the electronic submission*
679
680 The structure and content of electronic submissions to CBER should be based upon the
681 application (e.g., BLA and IND). Subsequent to the delivery of an electronic
682 application, any additional electronic information (i.e., amendments) will be added to
683 the existing copy of the submission residing in the Electronic Document Room (EDR).
684 BLA supplements are treated as separate submissions, not as continuations of the base
685 application. They will be stored in their own EDR folder. The root directory of an
686 electronic application should contain a roadmap.pdf file to orient the review team to the
687 application as well as subsequent information amending the application.

688 *Roadmap file*
689
690 CBER suggests that a roadmap.pdf file be used to establish hypertext links to an
691 application's or amendment's main table of contents and to the application folders and
692 files. If an application is submitted on multiple CDROMs or DLT tapes, each unit of
693 media should contain the identical roadmap.pdf file, which links to folders and files on
694 all of the media units. This *roadmap* file should be updated and resubmitted when
695 additional information is submitted to amend an application.

696 The roadmap.pdf file should be placed in the root directory of a submission. This
697 ensures that the outdated roadmap.pdf file is overwritten each time a new amendment is
698 loaded into the EDR. The roadmap file should not contribute in any way to the content
699 of the submission under review. It is a map, intended to facilitate navigation through the
700 contents of an application. The application's roadmap.pdf file should be easily updated
701 or modified, for example, using the Replace File command under the Document menu
702 option in Adobe Exchange. This function will automatically replace the old hypertext
703 links to previously submitted sections of the application, leaving only the task of creating
704 the new links corresponding to newly submitted information.

705 In addition to providing a navigable guide to the application, the roadmap.pdf file should
706 include the sponsor's submission date in the DD-MMM-YYYY format (e.g., 01-Jan-
707 1999). The contents of the original application and any subsequent amendments to that
708 application should be briefly described in a roadmap.pdf table. The location of these
709 files and folders on the submitted media should be indicated in the roadmap.pdf. Where
710 portions of an application have been submitted only as a paper documents, they should
711 be included in the roadmap and table of contents and tagged as *paper only*.

712
713 The following text is a representative example of a roadmap.pdf file.

714
715 # Electronic Roadmap
716
717

BLA Submission	Submission Date	Submission Content	CD-ROM	Hypertext link Destination
Sponsor Name	15-Jan-1999	FDA Form 356h .001		../blatoc.pdf
		cover.pdf	.001	
		BLA Table of Contents	.001	
		Item 01-Index	.001	
		Item 02-Labeling	.001	
		Item 03-Summary	.001	
		Item 04-CMC	.001	
		Item 05-Pharmtox	.001	
		Item 06-Cpbio	.001	
		Item 08-Clinical	.002	
		Item 10-Statistical	.002	
		Item 12-Crf	.002	
		Item 15-Estab	.002	
		Others (Items 13-16)	.002	
BLA 123456/5001/1	01-Apr-1999	cover.pdf`	.001	..\ 123456/5001/1\ amendtoc.pdf
		confid.pdf	.001	
		CMC	.001	
BLA 123456/5001/2	19-Jun-1999	Cover.pdf	.001	..\ 123456/5001/2\amendtoc.pdf
		Clinstat .001		
BLA 123456/5001/3	04-Jul-1999	cover.pdf	.001	..\ 123456/5001/3 \amendtoc.pdf
		confid.pdf	.001	
		Clinstat .001		
		Safety Update	.001	

718 719 720 721 722 723 724 725 726 727 728 729 730 731 732 733 734 735 736 737 738 739 740 741 742 743 744 745

746

747 *Summary File*

748

749 A summation of the electronic document, using at least 40 key words from the
750 main document, should be included with all electronic applications delivered to
751 CBER. This summation should be located in the root directory on the
752 CDROM or DLT tape. The file containing the key words should be an ASCII
753 text file entitled *Summary.txt*.

754

755 **CDER**

756

757 In general, when an electronic submission arrives in CDER, we copy the electronic files
758 to tape to create an archival copy of the submission. We also copy the files to a network
759 server to create a read-only copy for the reviewer. See specific submission type guidance
760 for additional details.

761

762   **CDRH**
763
764   Contact the appropriate reviewing division prior to making an electronic submission.
765   The division will inform you as to where and how to send submissions. Contacts can be
766   found at http://www.fda.gov/cdrh/organize.html#ODE. See individual guidance for
767   specific submission type for additional information.
768
769   **CFSAN**
770
771   When an electronic submission arrives in OFAS one copy of the media is archived: the
772   second copy of the submission's media is copied to a network server to create a read-only
773   copy for the reviewer.
774
775   The structure and content of electronic submissions to OFAS should be based upon the
776   application (e.g., Petition, Notification). Subsequent to the delivery of the electronic
777   application, any additional electronic and/or paper information will be added to the
778   existing network copy of the submission and made available to appropriate managers and
779   reviewers. The root directory of an electronic application should contain a roadmap.pdf
780   file to orient the review team to the original application and to any and all subsequent
781   information added to the application.
782
783   OFAS suggests that a roadmap.pdf file be used to establish hypertext links to the
784   application's main table of contents and to the application folders and files. This
785   *roadmap* or *home page* should be updated and resubmitted as additional information to
786   the application.
787
788   The roadmap file should not contribute in any way to the content of what is under review.
789   It is a map, intended to facilitate navigation through the contents of an application. The
790   application's roadmap.pdf file should be easily updated or modified, for example, using
791   the Replace File command under the Document menu option in Adobe Exchange. This
792   function will automatically replace the old hypertext links to previously submitted
793   sections of the application, leaving only the task of creating the new links corresponding
794   to newly submitted information.
795
796   In addition to providing a navigable guide to the application, the roadmap.pdf file should
797   include the sponsor's submission date in the DD-MMM-YYYY format.17 (e.g., 01-Jan-
798   2000). The contents of the original application and any subsequent amendments to that
799   application should be briefly described in a roadmap.pdf table. The location of these files
800   and folders on the submitted media should be indicated in the roadmap.pdf. Where
801   portions of an application have been submitted only as paper documents, they should be
802   included in the roadmap and table of contents and tagged as *paper onl*y.
803
804   A summation of the electronic document, using at least 40 key words from the main
805   document should be included with all electronic applications delivered to OFAS. This

806 summation should be located in the root directory on the CDROM or DLT tape. The file
807 containing the key words should be an ASCII text file entitled *Summary.tx*t.
808
809 **CVM**
810
811 We are developing procedures for processing electronic submissions sent on physical
812 media. See individual guidance for specific submission type for additional information.