INTERNATIONAL CONFERENCE ON HARMONISATION OF
TECHNICAL REQUIREMENTS FOR REGISTRATION OF
PHARMACEUTICALS FOR HUMAN USE

ICH M8 Expert Working Group

ICH eCTD v4.0 Implementation Package

DRAFT Specification for Submission Formats v.2.0

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26   ## DOCUMENT CHANGE HISTORY

Version	Date	Comments
2.0	13.November.2014	Draft version of Specification for Submission Formats document. This document is part of the Step 2 ICH eCTD v4.0 Implementation package.

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Table of Contents

1.   INTRODUCTION

This document describes the way files should be constructed for inclusion in the eCTD. This section includes file formats that are commonly used in electronic submissions. Other formats can be used according to guidance published in each region.

1.1   PDF

Adobe Portable Document Format (PDF) is a published format created by Adobe Systems Incorporated

(http://www.adobe.com). It is not necessary to use a product from Adobe or from any specific company to produce PDF documents. PDF is accepted as a standard for documents defined in this specification. The following recommendations support the creation of PDF files that agencies can review effectively. For any specification of the Japanese version of Adobe Acrobat, or where Japanese characters will be in the file, please refer to the regional guidance.

To ensure that PDF files can be accessed efficiently, optimize PDF files for fast web view.

1.1.1   Version

All ICH Regional Health Authorities are able to read and have agreed to accept PDF files saved as PDF version 1.4 through 1.7, PDF/A-1, or PDF/A-2. Agencies should not need any additional software to read and navigate the PDF files. Please consult regional guidance to submit other versions of PDF.

1.1.2   Fonts

PDF viewing software automatically substitutes a font to display text if the font used to create the text is unavailable on the reviewer's computer. Font substitution can affect a document's appearance and structure, and, in some cases, the information conveyed by a document. Agencies cannot guarantee the availability of any fonts except Times New Roman, Arial, and Courier and fonts supported in the Acrobat product set itself. Therefore, all additional fonts used in the PDF files should be embedded to ensure that those fonts would always be available to the reviewer. When embedding fonts, all characters for the font should be embedded, not just a subset of the fonts being used in the document

Embedding fonts requires additional computer storage space. Three techniques to help limit the storage space taken by embedding fonts include:

- Limiting the number of fonts used in each document

- Using only True Type or Adobe Type 1 fonts

- Avoiding customized fonts

Japanese fonts (2-byte fonts) are larger than Roman fonts (1-byte fonts), therefore, the specification allows a subset to be embedded for all Japanese fonts. The purpose of embedding fonts to is to enable the receiver of the document to use a personal computer to display and print the document correctly without having the same fonts installed in the computer. Therefore, it is not necessary to embed all Japanese fonts. Embedding a subset of Japanese fonts should work satisfactorily.

1.1.3   Definition of Subset

A subset means to embed only those characters used in the document. Embedding a full-set means all characters that comprise the font are embedded, even characters that are not used in the document. All two-byte fonts such as Japanese should be embedded as a sub-set.

Notes on Embedding Japanese Fonts:

The following should be considered when embedding fonts:

Advantages:

- Embedding fonts allows the PDF file to be correctly displayed and printed on any receiving PC environment.
- The computer does not need the original fonts installed.

Disadvantages:

- The file size increases when fonts are embedded.
- When document contains many pages, this can make the document slower to print.
- Many eCTD documents contain a large number of pages. Printing time in such cases becomes a concern.
- When using Japanese fonts, rules of operation should be established between the sender and receiver. (See regional guidance)
- The use of popular fonts only would allow the sender and receiver to view and print the document correctly without embedding fonts.

1.1.4   Font Size

Resizing a document because the contents are too small to read is inefficient. Times New Roman, 12-point font, the font used for this document, is adequate in size for narrative text and should be used whenever possible. It is sometimes tempting to use fonts which are smaller than 12 point in tables and charts but this should be avoided whenever possible. When choosing a font size for tables, a balance should be sought between providing sufficient information on a single page to facilitate data comparisons for the reviewer while maintaining a font size that remains legible. The corollary of this is that in using larger font size, more tables might be necessary, which can complicate data comparisons since data might now be included in separate tables. Generally, Times New Roman font sizes 9-10 or an equivalent size of other recommended fonts are considered acceptable in tables but smaller font sizes should be avoided.

1.1.5   Use of Color Fonts

The use of a black font color is recommended. Blue can be used for hypertext links. Light colors that do not print well on grayscale printers should be avoided. Color reproduction can be tested prior to submission by printing sample pages from the document using a gray scale printer. The use of background shadowing should be avoided.

1.1.6   Page Orientation

Pages should be properly oriented so that all portrait pages are presented in portrait and all landscape pages are presented in landscape. To achieve this, the page orientation of landscape pages should be set to landscape prior to saving the PDF document in final form.

1.1.7   Page Size and Margins

The print area for pages should fit on a sheet of A4 (210 x 297 mm) and Letter (8.5" x 11") paper. A sufficient margin (at least 2.5 cm) on the left side of each page should be provided to avoid obscuring information if the reviewer subsequently prints and binds the pages for temporary use. For pages in landscape orientation (typically tables and publications), smaller margins (at least 2.0 cm at the top and 0.8

cm left and right) allow more information to be displayed legibly on the page (see Fonts). Header and footer information can appear within these margins but should not appear so close to the page edge to risk being lost upon printing.

1.1.8   Headers and Footers

The M4 Granularity document specifies that all pages of a document should include a unique header or footer that briefly identifies its subject matter. With the eCTD there is a significant amount of metadata available to the reviewer to allow easy identification of the document but it is still appropriate to have a unique identifier on each page (header or footer) of the document (e.g., when the document is printed or multiple documents are viewed on screen at the same time). The unique identifier does not necessarily have to contain the CTD section identifier or other metadata. Inclusion of this information in the header/footer may complicate document reuse. It should be sufficient to identify the general subject matter of the document (e.g., study identifier, batch number).

1.1.9   Source of Electronic Document

PDF documents produced by scanning paper documents are usually inferior to those produced from an electronic source document. Scanned documents saved as image files are more difficult to read and do not allow reviewers to search or copy and paste text for editing. Scanning should be avoided where possible.

1.1.10   Methods for Creating PDF Documents and Images

The method used for creating PDF documents should produce the best replication of a paper document. To ensure that the paper and PDF version of the document are the same, the document should be printed from the PDF version. Documents that are available only in paper should be scanned at resolutions that will ensure the pages are legible both on the computer screen and when printed. At the same time, the file size should be limited. It is recommended that scanning be undertaken at a resolution of 300 dots per inch (dpi) to balance legibility and file size. The use of grayscale or color is discouraged because of file size. After scanning, resampling to a lower resolution should be avoided.

When creating PDF files containing images, the images should not be downsampled. Downsampling does not preserve all of the pixels in the original. For PDF images, one of the following lossless compression techniques should be used:

165 • For lossless compression of color and grayscale images, use Zip/Flate (one technique
166 with two names). This is specified in Internet RFC 1950 and RFC 1951
167 (http://www.ietf.org/rfc/rfc1950.txt).

168 • For lossless compression of black and white images, use the CCITT Group 4 Fax
169 compression technique. It is specified as CCITT recommendations T.6 (1988) - *Facsimile*
170 *coding schemes and coding control functions for Group 4 facsimile apparatus.*

171 Paper documents containing hand-written notes should be scanned at a resolution of at least 300
172 dpi.

173 Hand-written notes should be done in black ink for clarity. Higher resolution is specifically
174 requested when scanning documents containing non-Western characters (e.g. Kanji); 600 dpi is
175 recommended.

176 For photographs, the image should be obtained with a resolution of 600 dpi. If black and white
177 photos are submitted, 8-bit grayscale images should be considered. If color photos are submitted,
178 24-bit RGB images should be considered. A captured image should not be subjected to non-
179 uniform scaling (i.e., sizing). Gels and karyotypes should be scanned directly, rather than from
180 photographs. Scanning should be at 600 dpi and 8-bit grayscale depth. Plotter output graphics
181 should be scanned or captured digitally at 300 dpi.

182 High-pressure liquid chromatography or similar images should be scanned at 300 dpi.

183 Applicants should validate the quality of the renditions.

1.1.11   Hypertext Linking and Bookmarks

185 Hypertext links and bookmarks improve navigation through PDF documents. Hypertext links can
186 be designated by rectangles using thin lines or by blue text as appropriate.

187 In general, for documents with a table of contents, bookmarks for each item listed in the table of
188 contents should be provided including all tables, figures, publications, other references, and
189 appendices. Bookmarks should follow hierarchical level and order of table of contents. These
190 bookmarks are essential for the efficient navigation through documents. The bookmark hierarchy
191 should be identical to the table of contents with no additional bookmark levels beyond those
192 present in the table of contents. Each additional level increases the need for space to read the
193 bookmarks. The use of no more than 4 levels in the hierarchy is recommended.

194 Hypertext links throughout the document to support annotations, related sections, references,
195 appendices, tables, or figures that are not located on the same page are helpful and improve
196 navigation efficiency.

197 Relative paths should be used when creating hypertext links to minimize the loss of hyperlink
198 functionality when folders are moved between disk drives. Absolute links that reference specific
199 drives and root directories will no longer work once the submission is loaded onto the Agency's
200 network servers.

201 When creating bookmarks and hyperlinks, the magnification setting *Inherit Zoom* should be used
202 so that the destination page displays at the same magnification level that the reviewer is using for
203 the rest of the document.

204 There is no formal guidance on whether bookmarks should be presented expanded or collapsed.
205 It might not be considered appropriate to have all the bookmarks open since, in some instances,
206 these can be so numerous that they are not useful to the review and can affect 'refresh' time in a
207 web-browser. Equally, it is probably not useful to have the bookmarks fully closed, since the
208 reviewer would always have to open them. It is recommended, therefore, that the applicant
209 consider the usefulness to the reviewers of how to present bookmarks and have some level of
210 consistency across similar document types within the submission.

1.1.12   Page Numbering

212 Only the internal page numbers of the document are expected (1-n). No additional page/volume
213 numbers running across documents are expected. It is easier to navigate through an electronic
214 document if the page numbers for the document and the PDF file are the same. To accomplish
215 this, the first page of the document should be numbered page 1, and all subsequent pages
216 (including appendices and attachments) should be numbered consecutively with Arabic
217 numerals. Roman numerals should not be used to number pages (e.g., title pages, tables of
218 contents) and pages should not be left unnumbered (e.g., title page.) Numbering in this manner
219 keeps the Acrobat numbering in synchrony with the internal document page numbers.

220 The only exception should be where a document is split because of its size; the second or
221 subsequent file should be numbered consecutively to that of the first or preceding file. Refer to
222 Regional/Module 1 Implementation Guide for the maximum file size allowed in the region.

1.1.13   Initial View Settings

224 The initial view of the PDF files should be set as *Bookmarks* and *Page*. If there are no
225 bookmarks, the initial view as *Page* only should be set. The *Magnification* and *Page Layout*
226 should be set as default.

1.1.14   Security

228 No security settings or password protection for PDF files should be included. Security fields
229 should be set to allow printing, changes to the document, selecting text and graphics, and adding
230 or changing notes and form fields. Refer to Regional/Module 1 Implementation Guide for
231 additional information.

1.1.15   Use of Acrobat Plug-Ins

233 It is appropriate to use plug-ins to assist in the creation of a submission. However, the review of
234 the submission should not call for the use of any plug-ins in addition to those provided with
235 Adobe Acrobat because agencies will not necessarily have access to the additional plug-in
236 functionality.

1.2   XML Files

238 A working group at the World Wide Web Consortium (W3C) developed XML. It is a
239 nonproprietary language developed to improve on previous markup languages including standard
240 generalized markup language (SGML) and hypertext markup language (HTML).

241

242 XML is currently used for some content of the eCTD. The applicant should contact the
243 applicant's own regional regulatory authority, understanding that other regulatory authorities may
244 not accept these XML files.

245 Additional information about the XML standard can be found at the W3C Web site at
246 www.w3.org.

1.3   SVG Files

248 SVG is a language for describing two-dimensional graphics in XML. SVG allows for three types
249 of graphic objects: vector graphic shapes (e.g., paths consisting of straight lines and curves),
250 images, and text. Graphical objects can be grouped, styled, transformed and composited into
251 previously rendered objects. Text can be in any XML namespace suitable to the application,
252 which enhances searchability and accessibility of the SVG graphics. The feature set includes
253 nested transformations, clipping paths, alpha masks, filter effects, template objects, and
254 extensibility.

255 SVG drawings can be dynamic and interactive. The Document Object Model (DOM) for SVG,
256 which includes the full XML DOM, allows for straightforward and efficient vector graphics
257 animation via scripting. A rich set of event handlers such as onmouseover and onclick can be
258 assigned to any SVG graphical object. Because of its compatibility and leveraging of other Web
259 standards, features like scripting can be done on SVG elements and other XML elements from
260 different namespaces simultaneously within the same Web page.

261 The specific use of SVG in a submission should be discussed with the regulatory authority.

262 Additional information about the SVG specification can be found at the W3C Web site at
263 www.w3.org.