INTERNATIONAL COUNCIL FOR HARMONISATION OF TECHNICAL REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE

ICH M8 Expert Working Group

Specification for Submission Formats for eCTD

v1.2

June 5, 2018

DOCUMENT CHANGE HISTORY

Version	Date	Comments
1.0	10 December 2015	Initial Step 4 document.
1.1	10 November 2016	Revisions based on M8 Review and the following change requests: 00020, 00030 and 00050.
1.2	05 June 2018	Revisions incorporating the updates to the ICH M2 Expert Working Group Specification for PDF Formatted Documents in Regulatory Submissions.

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1. INTRODUCTION

This specification 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.

The content in this document should be used in conjunction with the regional specification documents for additional information.

2. PDF

Portable Document Format (PDF) is a published format compliant to the International Organization for Standardization (ISO) standard ISO 32000-1:2008. 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 regulatory authorities can review effectively, and is based on the ICH M2 Expert Working Group Specification for PDF Formatted Documents in Regulatory Submissions document.

2.1 Restrictions

In order to be usable, PDF files must not contain JavaScript, dynamic content (e.g., audio, video or special effects), attachments or 3D content. You should not include PDF annotations in documents.

2.2 Version

Currently recommended versions of PDF are listed on the ICH website (see http://estri.ich.org/recommendations for details). Submitted PDF files should be readable by Adobe Reader or Acrobat (versions 8 or higher) and should not require additional software or plug-ins to be read and navigated. If plug-ins are used during the creation of a PDF document, prior to submitting the document, you should ensure that a plug-in is not required to open, view or navigate the file.

2.3 File Size

The size of a PDF file should not exceed 500MB. Larger files should be split into smaller components.

2.4 Fonts

PDF viewing software automatically substitutes a font to display text if the font used to create the text is not provided with the PDF or is unavailable on the viewer's computer. Font substitution can affect a document's appearance and structure, and, in some cases, the view of the document contents may be affected. The following should be followed when creating PDF files:

- Embed all fonts used in the PDF
- Use only OpenType or TrueType fonts

- Avoid using customised fonts

Font embedding does not always solve the problems that occur when a viewer tries to copy and paste text from a PDF document into another software format. The fonts listed in Table 1 are preferred:

Table 1 – Preferred Fonts

Font type	**Font Name**
Serif	Times New Roman
	Times New Roman Italic
	Times New Roman Bold
	Times New Roman Bold Italic
Sans Serif	Arial
	Arial Italic
	Arial Bold
	Arial Bold Italic
Non Proportional	Courier New
	Courier New Italic
	Courier New Bold
	Courier New Bold Italic
Other	Symbol
	Zapf Dingbats
Japanese	MS Mincho
	MS Gothic
	Chu-Gothic
	Sai-Mincho

2.4.1 Font Size

You should use font sizes ranging from 9 to 12 points. Times New Roman, 12-point font, the font used for this document, is adequate in size for narrative text and should be used. 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 viewer while maintaining a font size that remains legible. Generally, Times New Roman font sizes 9-10 or an equivalent size of other recommended fonts are considered acceptable in tables and smaller font sizes should be avoided. Ten-point fonts are recommended for footnotes. MS Mincho, 10.5-point font should be used for narrative text whenever possible in Japan. Font sizes of 8pt and larger can be used in figures and tables.

2.4.2 Use of Colour Fonts

The use of a black font colour is recommended. Blue can be used for hypertext links. Light colours can be difficult to read on a monitor as well as when printed, and should be avoided. The use of background shading can be difficult to read and should be avoided.

2.5 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.

2.6 Page Size and Margins

The print area for pages should fit on both a sheet of A4 (210 x 297 mm) and Letter (8.5” x 11”) paper. A sufficient margin of at least 2.5 cm on the binding edge (i.e., the left side of each page for portrait and top of the page for landscape) should be provided to avoid obscuring information when documents are printed and bound. The remaining margins should be a minimum of 1.0 cm. Header and footer information and page numbers should not appear in margins.

2.7 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. It should be sufficient to identify the general subject matter of the document (e.g., study identifier, batch number).

2.8 Source of Electronic Document

You should avoid image-based PDF files whenever possible. PDF documents produced by scanning paper documents usually have poorer image resolution than PDF documents produced from electronic source documents such as word processing files. Scanned documents are generally more difficult to read and do not allow the viewer to search or copy and paste text for editing in other documents. If scanned files must be submitted, they should be made text searchable where possible. If optical character recognition software is used, you should verify that imaged text is converted completely and accurately.

2.9 Recommendations for Creating PDF Documents and Images

You should use the dpi settings in Table 2 for scanning documents. Scanned documents scanned at a resolution of 300 dots per inch (dpi) ensure that the pages of the document are legible both on the computer screen and when printed and, at the same time, minimises the file size. After scanning, you should avoid resampling to a lower resolution. A captured image should not be subjected to non-uniform scaling (i.e., sizing). See the Table 2 for resolutions recommended for various image types.

Table 2 - Scanning Resolutions

Document type	Resolution
Handwritten notes	300 dpi (black ink)
Plotter output graphics	300 dpi
Photographs – black and white	600 dpi (8-bit Gray scale)
Photographs – colour	600 dpi (24-bit RGB)
Gels and karyotypes	600 dpi (8-bit grayscale depth)
High pressure liquid chromatography	300 dpi

2.10 Image Compression to Reduce File Size

You should compress colour or grayscale images using JPEG 2000 and use JBIG2 for monochrome images. Image compression is a method for reducing file size. Some methods of compression can result in loss of data and can introduce compression artefacts that affect the reviewability of the information. Both compression methods have lossless options.

2.11 Image Colour Matching

Because colour varies from monitor to monitor, it is difficult to ensure that the reviewer will see exactly the same colour as in the original image. To avoid this discrepancy, you should use ICC profiles for colour matching (The International Color Consortium (ICC) – www.color.org).

2.12 ICC Profiles

This standard format is used to characterize the colour properties from input devices (cameras, scanners), viewing devices (monitors) and finally output devices (colour printers, print processes).

ICC profiles are defined by the International Color Consortium. There is also an ISO standard (ISO 15076). ICC profiles are used in PDF for defining ICC-based colours and as output intents (OutputIntent).

2.13 Document Navigation (Hypertext Linking, Bookmarks and TOCs)

Hypertext links and bookmarks improve navigation through PDF documents. Hypertext links can be designated by rectangles using thin lines or by blue text as appropriate. Bookmarks are expected even if there is no table of contents (TOC) in the document. A hypertext linked TOC and bookmarks should be included in documents 5 pages or longer. Literature References are the exception to these recommendations as the files may be protected and cannot be modified.

In general, for documents with a table of contents, bookmarks for each item listed in the table of contents should be provided. Bookmarks should include all tables, figures, publications, other references, and appendices even if these items are not in the table of contents. These bookmarks are essential for the efficient navigation through documents. The use of no more than 4 levels in the hierarchy is recommended, but additional levels could be created if such bookmarks contribute to efficient navigation.

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

Relative paths should be used when creating hypertext links across documents to minimize the loss of hyperlink functionality when folders are moved between disk drives. Absolute links that reference specific drives and root directories will no longer work once the submission is loaded onto the receiving party's computers.

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

The bookmarks should be collapsed when document is opened so that all bookmarks are at the first level. Also, see Section 2.15 for Initial View Settings.

2.14 Page Numbering

It is easier to navigate through an electronic document if the page numbers for the document and the PDF file are the same. To accomplish this, the first page of the document should be numbered page 1, and all subsequent pages (including appendices and attachments) should be numbered consecutively with Arabic numerals. Roman numerals should not be used to number pages (e.g., title pages, tables of contents) and pages should not be left unnumbered (e.g., title page.) Numbering in this manner keeps the PDF viewer page in synchrony with the internal document page numbers.

The two exceptions to these recommendations are:

- When a document is split because of its size (Refer to Section 2.3 File Size); the second or subsequent file should be numbered consecutively to that of the first or preceding file, and
- Literature References as the files may be protected and cannot be modified.

2.15 Initial View Settings

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

2.16 Optimisation

To ensure that PDF files can be accessed efficiently, you should optimise PDF files for fast web view.

2.17 Security

No security settings or password protection for PDF files should be included. Security fields should be set to allow printing, changes to the document, selecting text and graphics, and adding or changing notes and form fields. The exception to this rule includes regulatory forms

with pre- existing security and literature references that need to be copyright protected. At a minimum the receiver should be able to easily open and view the content.

2.18 Use of Acrobat Plug-ins

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

3. XML FILES

A working group at the World Wide Web Consortium (W3C) developed the Extensible Markup Language (XML). It is a nonproprietary language developed to improve on previous markup languages including Standard Generalized Markup Language (SGML) and Hypertext Markup Language (HTML).

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

Additional information about the XML standard can be found at the W3C Web site.

4. SVG FILES

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

SVG drawings can be dynamic and interactive. The Document Object Model (DOM) for SVG, which includes the full XML DOM, allows for straightforward and efficient vector graphics animation via scripting. A rich set of event handlers such as onmouseover and onclick can be assigned to any SVG graphical object. Because of its compatibility and leveraging of other Web standards, features like scripting can be done on SVG elements and other XML elements from different namespaces simultaneously within the same Web page. SVG files must not contain JavaScript.

The specific use of SVG in a submission should be discussed with the regulatory authority. Additional information about the SVG specification can be found at the W3C Web site.

5. STUDY DATASET FILES

Specific regions include study datasets and may have different rules regarding the following topics:

- Allowable file formats
- Dataset file sizes
- Dataset filenames and allowable characters