



Templates: Taking the first step towards eCTD submissions in Europe

by Peggy Boe

The Common Technical Document (CTD) has been the mandatory marketing application format for submissions in the European Union (EU) since 2003. At a recent Drug Information Association (DIA) conference in the United States, a representative of the European Medicines Agency (EMA) announced plans to accept submissions in the electronic Common Technical Document (eCTD) format without accompanying paper beginning late in the 4th quarter of 2006 [1]. While there are several national authorities in Europe accepting eCTDs, most still require paper as the archival format. With this in mind, sponsors should continue to carefully discuss submission format with the appropriate regulatory authority before finalizing any decisions on whether to submit in paper or to take the next step and submit electronically [1]. Europe has targeted late 2009 for all regulatory authorities to have the capability of accepting “paperless” electronic submissions.

There is a substantial difference between the eCTD and the paper CTD beyond what most people think of as an electronic submission. In the case of the eCTD, the “e” stands for more than just “electronic”; it represents inclusion of a backbone (similar to an overall submission table of contents [TOC]) that is based on the extensible mark-up language (XML). Creation of the XML backbone requires special skills or use of software typically beyond the scope of regulatory and medical writers. More often than not, sponsors are using publishing groups (either internal or outsourced), who are most knowledgeable in the eCTD software, to import final submission documents into the appropriate place in the XML backbone. Writers may be called upon to assist in determining the appropriate placement of individual documents based on content. Also, writers can facilitate the electronic-publishing process overall by standardizing the way documents are formatted, to make them ready for publishing. Ultimately, every narrative document in the submission (with the exception of original signature pages and certain labelling documents) needs to be submitted in PDF format with extensive navigational aids included (fully hyperlinked and bookmarked). Writers should understand what can be done to

make life easier for themselves and others who process the documents.

The first and most important step any regulatory submission writer can take towards preparing documents for an eCTD is to use a submission-compliant template to create each document. But what exactly is a template? According to the Merriam-Webster Online Dictionary, a template is defined as, among other things, “something that establishes or serves as a pattern” [2]. In the case of a word-processed document, a template could be a basic outline for the writer to complete, which helps with content but does nothing to support compliance with format specifications. As a general international guideline, “the display of information should be unambiguous and transparent, in order to facilitate the review of the basic data and to help a reviewer become quickly oriented to the application contents. Text and tables should be prepared using margins that allow the document to be printed on both A4 paper (EU and Japan) and 8.5 x 11 papers (United States [US]). The left-hand margin should be sufficiently large that information is not obscured by the method of binding. Font sizes for text and tables should be of a style and size that are large enough to be easily legible, even after photocopying. Times New Roman 12-point font is recommended for narrative text. Every page should be numbered, according

to the granularity document”[3]. Those recommendations apply to paper or electronic submissions, because even with electronic submissions reviewers want the option of printing and binding portions of the submission.

US guidance offers more specifics on format; for example, they recommend using nothing smaller than 9-point font in in-text tables,

Submission-compliant templates for creating each document are important for a medical writer in preparing documents for an eCTD.

and settings are specified for the PDF conversions [4]. without standards, the format of a document is largely dependent on personal preference and can vary widely from one document to another, depending on the writer. What is not transparent to the writer is that MS Word applies its own “Normal.dot” file to every document. The Normal.dot file applies three unnumbered heading styles

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>>> Templates for eCTD submissions

and a paragraph text style (also called “Normal”), pre-programmed for the writer to use consistently (.dot is the file extension for the Word Document Template associated with MS Word for Windows). Working within a Normal.dot template requires a writer to build additional styles from scratch, using whatever font sizes and styles, margins, indents, list styles, etc. that the writer prefers. Depending on the settings, MS Word may arbitrarily create new styles for the writer. Additional styles are frequently imported from other documents whenever the writer copies and pastes from another source; thus, the format of documents generated by different writers may vary immensely. MS Word will also “help” the writer format the document whether help is wanted or not, in ways that add significant time and effort to the writing and quality control processes as the writer tries to “fix” what MS Word has done automatically.

Document styles are important for reasons other than aesthetics and compliance with font and margin specifications. To be electronic-submission compliant, hyperlinks and bookmarks are required for the entire TOC and elsewhere. If inserted correctly, heading styles will automatically generate the TOC and automatically create the TOC hyperlinks and bookmarks when the document is converted to PDF. If inserted incorrectly, those hyperlinks and bookmarks must be created manually by the publishing group. Therefore, an outline alone with the Normal.dot template supplied by MS Word does not suffice to ensure compliance with submission-ready formatting specifications and results in a lot of extra work for the writer or publishing team.

The solution to this problem is for sponsors to adopt a policy of using a set of templates that are programmed to conform to agency specifications. These templates could be developed in-house, but that requires a significant amount of time and effort. Therefore, many sponsors are opting to use software and service providers who have already developed templates and who will maintain the templates as guidances and regulatory requirements change. Such customized .dot templates can supply guidance-compliant styles and additional goodies, such as tools to prevent MS Word from automatically changing numbered lists, to repair unwanted styles, to facilitate printing on either 8.5 x 11 inch letter size or A4 paper without shifting the text on any pages, and to automatically populate

MS Word applies its own “Normal.dot” file to every document.

repeatable text. If a sponsor does decide to purchase a set of templates, the features and help aids should be evaluated to see whether they include adequate features to make the writing process easier.

Templates can also assist with creating guidance-compliant content by keeping writers informed of recommended text for inclusion in various sections of the CTD. The inclusion of writing aids, such as instructional text, can help ensure inclusion of appropriate content. In some templates, instructional text can be deleted or hidden, either totally or in pieces as a writer completes each section. As an additional bonus, templates can help writers prepare content according to the required CTD granularity. International Conference on Harmonisation (ICH) guidelines describe options for CTD granularity, and sponsors are encouraged to submit documents using finer levels of granularity when transitioning from paper to eCTD submissions to benefit from the advantages of submission lifecycles. One ICH guideline specifies that “when relevant information is changed at any point in the product’s lifecycle, replacements of complete documents/files should be provided in the CTD and eCTD.” Furthermore, a document is defined

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as “...a set of pages, numbered sequentially and divided from other documents by a tab” (for a paper submission), and “a document can be equated to a file for an electronic submission. The granularity of the paper and electronic submissions should be equivalent...In an elec-

tronic submission, a new file starts at the same point at which, in a paper submission, a tab divides the documents”[5]. Therefore, the replacement process is simplified if sponsors take advantage of using the highest level of granularity with the initial submission, and templates provided in full granularity ease the writer’s burden of determining the breakdown of once-familiar larger documents.

Another granularity specification that writers should be aware of includes a difference between paper and eCTD TOCs: the various TOCs for each CTD module (Modules 2 to 5) are necessary in a paper submission but are not required in an eCTD. The XML backbone replaces the need for TOCs in those modules. Be careful not to misinterpret that point; eliminating modular TOCs does not mean that individual documents do not require TOCs. Some common sense should prevail when generating any document. There is no formal definition of what constitutes the need for a TOC. In general, if a document has multiple sections and spans more than a couple of pages, including a TOC may be a good idea. Always keep the reviewer in mind and simplify the reviewer’s ability to navigate through an individual document. Under no circumstances should a large document be submitted without a TOC; a refusal to file might result.

Templates for eCTD submissions

Templates available on the market today may or may not include TOCs for various documents. This is an example of how a sponsor's internal regulatory knowledge (and again, common sense) is important when implementing templates for part or all of the submission documents. The other knowledge-based factor that cannot be included in any package of templates is the decision process appropriate for what content to include (and in what granularity) for a particular product, development programme, and type of submission. By no means should templates be considered the replacement for a sponsor's internal regulatory affairs knowledge base.

In conclusion, templates can improve document quality through consistent, regulatory-compliant formatting, can add to the understanding of recommended content, and can decrease the amount of time normally spent on formatting and quality control, thereby allowing writers to focus on the science and interpretation of data. eCTD submissions begin with document generation and preparation; document generation and preparation begin with a solid template.

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Some English scientific words?

Starting simply.

Chasing a chimera

Greek (chimaira): a creature that merges features of more than one beast. The mythical Greek Chimera had the head of a lion, body of a goat and hindquarters of a dragon. Because the uncertainty of her form made her difficult to paint she has come to represent an impossible idea or hope.

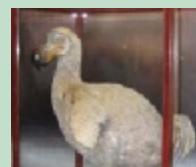
English scientific: a chimera is an organism comprising tissues of two or more genotypes.

NB a chimere (not chimer) is a bishop's upper robe.

Almost as mythical is the dodo.

As dead as a dodo

Portuguese (doido): fool or mad in modern Portuguese. In archaic Portuguese it was the name for a "simpleton".



Scientific English: a common name for the extinct bird *Didus ineptus*. Although Dutch settlers were responsible for the dodo's extinction Portuguese sailors were the first to visit Mauritius in 1505. By sometime between 1681 and 1693 not one dodo was left, except a stuffed one at the Ashmolean Museum in Oxford. But only until 1755 when the museum director decided it was a bit tatty and had it thrown on a bonfire. An employee tried to rescue it from the fire but was only able to save its head and part of a limb. Hence we know little about this flightless pigeon and had it not been brought to fame by a character in Lewis Carroll's *Alice's Adventures in Wonderland* probably none of us would be saying "as dead as a Dodo" today. All is no longer lost since Dutch geologists found a cache of dodo remains in December 2005 raising hopes of reconstructing the bird and its habitat.

And really quite confusing is chow.

Chow

Chinese (chiao): dough filled with meat. Chow Chow (*Chau-chau*): a Chinese dog with a tail curved over its back. Chow-chow (pidgin English): a Chinese mixed preserve.

Scientific English: John Kirkman in an article in the *BMJ* (1996;313:1321-3), which urged contributors to medical journals to confine themselves to forms of English that are easily understood, wondered whether a Frenchman would understand "All animals were fed standard laboratory chow". The Frenchman's initial dictionary searches would lead him to conclude the animals were eating British English grub or nosh (with deeper searches he would find the French equivalent bouffe). A British soldier might be even more confused though as chow is a military synonym for cat.

And with that thought 'chow' as the Italians would say.