

Meeting Report

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DATE: November 26, 2008

TO: Beckloff Associates, Inc., File

FROM: Greg A. Onyszchuk, Ph.D.

SUBJECT: Meeting Report—DIA 7th Annual Electronic Submissions Conference, eCTD: The Adventure Continues

MEETING DATE: November 6-7, 2008

MEETING LOCATION: San Diego, California

PARTICIPANTS: Greg A. Onyszchuk, Ph.D., Beckloff Associates, Inc.

Summary

The DIA 7th Annual Electronic Submissions Conference was sponsored by the Drug Information Association. Speakers from FDA and the pharmaceutical industry presented on topics related to electronic submissions and in particular the electronic Common Technical Document (eCTD) format. The objectives of the conference were to describe “practical experience gained, lessons learned, and resulting best practices as the industry moves to a fully electronic submission paradigm”. Sessions in the conference included:

Presentations by Regulatory Agency Personnel:

- eCTD Progress Report: an overview and progress report on eCTDs and electronic submissions on the US, Canada and Europe
- FDA Insight: best practices information for submitting information to the FDA in the eCTD format

Presentations by Industry Adopters and Experts

- The Switch to eCTD / Getting Started: case studies of eCTD adoption by pharmaceutical companies
- Outsourcing Solutions: practical examples of using outsourcing to maximize efficiency in eCTD and Regulatory Operations
- Strategies for US and Global eCTD Submissions: tactical strategies for initiating global eCTDs and handling regional disparities
- All-Electronic Publishing: perspectives on moving to or implementing eCTD publishing

eCTD Progress Report – US Update

This presentation was given by Gary Gensinger, Deputy Director, FDA CDER Office of Business Process Support. The highlights are provided below.

- data show 31% of NDA originals this year have been received in eCTD format, compared to 4% of IND originals, and the comment was made that the FDA would like more progress in the IND area.
- In the month of October 2008, the FDA received over 3000 eCTD “sequences”, and the volume continues to climb.
- The next evolution in electronic submission standards, the Regulated Product Submission (RPS), is of great interest to the FDA is expected to be released in 2 versions for *trial use*, RPS2L1 (Lifecycle 1) in January 2010, and RPSL2 (Lifecycle 2) 6 to 24 months later. The potential implementation of RPSL1 was given as September 2011. No information was given about RPS becoming mandatory nor about the period of time during which eCTD and RPS may both be acceptable formats.
- One of the key differences between RPS and eCTD is that RPS enables two-way information flow, and so could potentially enable electronic flow of information from the agency to the sponsor. This may assist the FDA in accomplishing its PDUFA performance goals.
- A reminder was given that Electronic Drug Establishment Registration and Drug Listing Information must be provided in electronic SPL r4 format, beginning June 1, 2009. *This is an important deadline, establishing a requirement for electronic filing of information for any owner or operator of an establishment engaged in the manufacture, preparation, propagation, compounding, processing, repackaging or relabeling of drugs. Paper submission of this information, currently done via Forms FDA 2656, FDA 2657, and FDA 2658, will not be accepted unless a waiver has been granted.*
- In response to an audience question, no timeline was given for when eCTD may become mandatory in the United States, *however in several informal discussions following this presentation, other conference participants indicated that they are not waiting for the FDA to make eCTD mandatory, but are proactively adopting the format and in some cases are being requested by FDA reviewers to submit in eCTD instead of paper.*

eCTD Progress Report – European Update

This presentation was given by Rob de Haan, Deputy Director, Medicines Evaluation Board of the Netherlands. The highlights are provided below.

Netherlands Highlights:

- as of April 2008, the Netherlands MEB has made e-submissions mandatory, and as of September 2008, they are receiving less than 1% of submissions on paper (*there are some grandfathered categories*).
- the MEB accepts both eCTD and NeeS (non-eCTD electronic submission) formats.
- the NeeS format is very similar to the eCTD, but lacks the xml backbone. The MEB, in deciding to accept this format, was able to choose an earlier date to mandate electronic-only submissions.

Europe Highlights:

- per the EMEA survey conducted earlier this year, only 23% of European agencies were ready for eCTD MAA's.
- of those not ready, 13% planned to become ready in 2008, 47% in 2009. *Therefore, by end-2009, about 70% of agencies will be ready.*
- recent data indicate 100% of Centralized Procedure MAAs are being submitted electronically, approximately 60% in eCTD format, and 40% in NeeS format. Also, 100% of variations and renewal applications under the Centralized Procedure are being submitted electronically.

eCTD Progress Report – Canadian Update

Most of this presentation was prepared by representatives from Health Canada. The highlights are provided below.

- Health Canada currently allows two submission formats: co-submission, which is a complete paper CTD and a complete eCTD, and hybrid, which is a paper CTD of Modules 1 and 2 plus a complete eCTD.
- No date has been announced for when eCTD-only submissions will be accepted.

- Submissions to Health Canada which included an eCTD component were 6% of the total received in the first half of 2008. Expectations are for eCTD to be part of 10% of total submissions for the full year 2008, and that by 2010, this will rise to 25%.
- It was noted that Health Canada validation criteria for eCTDs are different from those for the FDA, that 4.4% of eCTD's submitted in the first half of 2008 failed validation.
- Most frequent errors in submissions failing validation were: inactive bookmarks, inactive hyperlinks, external links (which are not permitted in Canadian submissions), and incorrect naming of Form 3011.
- The following submission types are currently under consideration by Health Canada for electronic format: Clinical Trials Authorization (CTA), Drug Identification Number (DIN) and Drug Master File (DMF).

FDA Insight – FDA Considerations for eCTD INDs

This presentation was given by Connie Robinson-Kuiperi, FDA CDER Office of Business Process Support. The highlights are provided below.

- It was reiterated that the eCTD is the format that is preferred by the FDA.
- Additionally, it was mentioned that most FDA reviewers prefer the eCTD to the paper format.
- Reviewability and navigation are very important to reviewers (accomplished by bookmarks and links).
- The use of scanned images was specifically discouraged, since it aggravates reviewers, makes the preparation of their reviews more difficult, and can impede reviews.
- The practice of sending “electronic desk copies” was also specifically discouraged.
- Among examples of common issues with eCTD IND's: insufficient bookmarking, identical titles in successive leaf nodes, poorly constructed study file titles that convey no useful information.
- This speaker closed with a comment that many of the common issues with eCTD IND applications reflect an inadequate quality assurance and quality checking (QC) process.

FDA Insight – Effective Use of eCTD Module 3 for Communicating Complex CMC Information

This presentation was given by Norman Schuff, FDA CDER Office of New Drug Product Assessment. The highlights are provided below.

- Especially for CMC amendments, the use of a table or opening paragraph, to highlight changes in documents where material is appended or replaced was recommended.
- Additional detailed suggestions: ensure that all pages are numbered, ensure that there is identity information contained in footers, place DMF Letters of Authorization in Module 1 (not in Module 3), do not include shelf-life specifications in the stability section, prepare 2 separate 3.2.S sections when there are 2 drug substance manufacturers, use short descriptive backbone file titles to improve reviewability.
- This speaker made a comment that for eCTD IND submissions, in particular for the CMC sections, it is not necessary to follow the eCTD granularity requirements. Reducing granularity would allow avoiding a submission with many small files. *This comment was not well-received by the audience - in the subsequent question and answer period, audience members questioned the reduced granularity idea and pointed out that for lifecycle management of submissions, and for ease of updates to CMC sections, full granularity enables simpler updates and amendments.*

FDA Insight – Implications of Errors in eCTD Submissions

This presentation was given by Don Duggan, FDA CDER Office of Business Process Support. The highlights are provided below.

Most common errors in eCTD submissions received at the FDA:

- duplicate submissions through the electronic gateway,
- truncated file names,
- hyperlink problems (can result in an Refuse To File),
- submissions sent to wrong center: CBER/CDER,
- no us-regional.xml file,
- entire submission as one .pdf file (this would be rejected),
- incomplete or missing application # in us-regional.xml file,
- mismatch between application type, forms, and us-regional.xml file content,
- use of non-fillable pdf forms (requires manual processing, introduces delay),
- spaces or other unacceptable characters in file names or folders,
- us-regional.xml file created in Notepad or Excel (can not be processed by the FDA).

This last error – unprocessable us-regional.xml file - may reflect that some sponsors are attempting to prepare eCTD submissions without a full-strength publishing system. The us-regional.xml file is a critical backbone of every eCTD submission and must have appropriate structure and metadata for successful processing at the FDA.

- The closing comment by this presenter was that “formal, standardized processes are essential for avoiding eCTD errors”.

Selected General Highlights from Industry Adopter and Expert Presentations

- Pharmaceutical and biotech companies, large and small, are adopting the eCTD format.
- In many cases, implementation of the eCTD involves two parallel initiatives: one to redesign processes and one to implement the technology or establish the outsourcing arrangement.
- Successful eCTD implementation projects often involve extensive communication and process design work to enable authors to focus on content and regulatory resources to focus on structure, format and compliance.
- Successful eCTD adoption often involves extensive use of project planning and project management.
- Success frequently involves full commitment to follow processes and to respect time frames. The notions of “locking” tables of contents, and of declaring that documents are truly “final”, were described as important challenges for organizations to learn and build in to their processes.
- Once a sponsor has established eCTD capability, this format rapidly becomes the preferred format for the organization for new original submissions.
- In addition to responding to FDA preference, additional benefits of eCTD adoption were given as follows:
 - Improved submission preparation processes,
 - Improved standards, consistency and submission document quality through the use of templates and tools,
 - Enhanced visibility to projects during due diligence activities,
 - Ability to prepare portions of submissions far in advance when certain content is ready early,
 - Reduced time for following a U.S. filing with a filing in another jurisdiction

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