

# Meeting Report

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**TO:** Beckloff Associates, Inc., File

**FROM:** Greg A. Onyszchuk, Ph.D.

**SUBJECT:** Meeting Report—DIA 22<sup>nd</sup> Annual Conference for Electronic Document Management and eCTD

**MEETING DATE:** February 11-13, 2009

**MEETING LOCATION:** Philadelphia, PA

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## Meeting Summary

The DIA 22<sup>nd</sup> Conference for Electronic Document Management and eCTD was sponsored by the Drug Information Association. Speakers from regulatory agencies, the pharmaceutical industry, and information technology companies presented on topics related to electronic document management (EDM), electronic submissions and in particular the electronic Common Technical Document (eCTD) and the Regulated Product Submission (RPS). The objectives of the conference were to “help unravel and clarify how both document/information management and submission technology play a central role in the pathway from research to submission”.

Five important themes that resonated throughout the conference presentations were:

- 1 – embrace and adoption of the eCTD format continues to be strong, in the U.S. and in the EU;
- 2 – the FDA Electronic Submissions Gateway (ESG) is a key infrastructure element to speed submissions to reviewer desktops;
- 3 – the Regulated Product Submission (RPS) standard is seen as the next logical evolutionary step after eCTD towards richer, two-way interactions between sponsors and agencies;
- 4 – more effective collaborations around drug development and regulatory submissions are being achieved by the implementation of electronic technologies and systems;
- 5 – emerging standards and paradigms promise greater efficiency in clinical trial data capture and management, paving the way for sustainable, sharable data repositories.

Summaries of some of the individual sessions are provided below. In each case, interpretation and business impact commentary are provided in italics.

## **Session Summaries**

### **Business Processes, Workflows and Collaboration Sessions:**

#### Collaboration: Document Authoring, Document Reuse, Submission Assembly

To help ease the challenge of internal/external authors, managing submission documents, and operating in a global environment, it is important to find a solution that will merge needs of a controlled Document Management System (DMS) with users in a more fluid environment. Basically, let your eDMS be a wrapper for a collaborative site so your company can control access and permissions for internal/external users while using the audit controls of your eDMS. Using a centralized DMS will alleviate multiple sites from working in silos and it will promote harmonization of document standards/formats across sites as well as document reuse. De-centralize workload and centralize information.

*Business bottom line: a centralized DMS can enable centralized information control while effectively supporting a de-centralized, collaborative work flow.*

#### Quality Throughout the Document Management Lifecycle

Updates to relevant regulations, QA/QC process to support and enhance these developments are a few of the challenges associated with Quality throughout the Document Management Life Cycle. It is also imperative that there is collaboration between the Document Management and Data Management groups. In addition, it is important that companies understand and implement 21 CFR Part 11 compliance and the upcoming changes. Several starting points are: preparing an assessment plan/process map, applying/analyzing system security, and performing a GAP analysis (i.e., answer the question, “Where are we versus where we need to be?”, then provide information needed to close the gap). And, when working through these challenges, remember that **Process Issues Block Work on Tasks (PIBWOT)**.

*Business bottom line: it is vital know the 21 CFR Part 11 requirements and document your compliance. Also, focus on content in the presence of automation and don't underestimate the training involved when implementing new Document Management System*

#### Metadata

You often hear the definition of metadata as data about data, so what does that mean and why is it so important? Metadata is used in documents, datasets, repositories, and submissions. In Microsoft Word or Adobe PDF documents, you find metadata in the Document Properties dialog box but it is unstructured and not easily accessible/changeable. In datasets, repositories, and submissions, you find metadata in the XML. By using the XML, metadata is structured...meaning it can be organized in places where it can be retrieved easily and definitely. Essentially, the metadata can be part of the document. There are three different types of metadata: descriptive (i.e. module 1 information such as sponsor name, application date/type), structural (i.e., application number, sequence number, module eCTD heading), and process (i.e., version, status, operation attribute). In the future, Regulated Product Submission revision 2

(RPS R2) will standardize the use of metadata, enable use of two-way communication, provide a single XML backbone (no more STFs and regional module 1 files), more flexible life cycles, and the ability to update multiple dossiers at once.

*Business bottom line: standardizing metadata is important for the future, and is expected to be a key feature of the Regulated Product Submission (RPS) standard. RPS can be considered an extension of eCTD with added capabilities.*

### Business Process Improvement Via Digital Signatures

In connection with developing a virtual collaboration system, organizations also need to evaluate the implementation and use of digital signatures. Digital signatures and electronic signatures are not synonymous. Digital signatures require some type of verification and/or certification of the signature to confirm the authenticity. A digital signature may be created using a software such as Adobe Acrobat or by purchasing a digital certificate, hardware token or other device used as a “key” to confirm the digital signature authenticity.

In contrast, an electronic signature may be a copy or a scan of a “wet” signature. The authenticity of an electronic signature is confirmed by either witnessing the actual signature or by comparing to a signature on file. The original “wet” signature should be maintained in an archive file.

*Business bottom line: the implementation of virtual collaboration workflows and digital signatures are increasingly necessary for pharmaceutical organizations to support the FDA initiatives for electronic submissions.*

### **Regulatory Updates:**

#### FDA Update on eCTD

Gary Gensinger provided an update of FDA statistics. As of May 31, 2006, CDER had received 285 eCTD applications and 3,358 eCTD sequences. As of February 9, 2009, the number of eCTD applications had increased to 5,049 and the number of eCTD sequences had increased to 53,970. In three years, these numbers represent annual average increases of over 250%! In January 2009, FDA received almost 3,000 eCTD submissions. The trend is very definitely in favor of electronic submissions.

Wendy Aronson shared that in February 2009, eCTD submissions accounted for 20% of all submissions received at CDER on a monthly basis. This is up from 10% less than two years earlier.

*Commentary: While short of a legislative mandate, there is very little doubt that eCTD enjoys a special status as the agency’s “preferred format” for submissions. This is rapidly becoming motivation enough for many sponsors to adopt eCTD.*

#### FDA Electronic Submission Gateway (ESG)

The ESG received priority treatment during the regulatory presentations.

Significant emphasis is being placed on the ESG due to the June 1, 2009 deadline for electronic submission of drug listing and drug establishment information, which requires these submissions to be sent via a connection to the ESG. Sponsors are encouraged to register for the ESG prior to the June 1, 2009 deadline. The process for ESG registration is as follows:

- Request submitted to [esgprep@fda.hhs.gov](mailto:esgprep@fda.hhs.gov) for a test account
- Send a Letter of Non-Repudiation to FDA
- Obtain a Digital Certificate
- Follow instructions at <http://www.fda.gov/esg/> to establish a test account and complete the testing process prior to establishing a production account

Activity through the ESG continues to increase. The following submissions were received through ESG in the first two months of 2009:

Adverse Events Reporting System (AERS): 40,292

CDER: 5,266

CBER: 518

CDRH: 1,512

CVM: 133

OC: 133

These numbers represent an increase of 129% over the same period in 2008.

as well as not sending paper for electronic submissions because the Central Document Room may not know how to process it and using paper can delay the process of getting submission to reviewers.

*Commentary: Several FDA presenters commented that the ESG is the “fastest way to get your submission in to the reviewers’ hands”. Content received this way is processed more rapidly once it arrives at FDA.*

### FDA Processing Times

Material was presented to describe how there can be quite a large difference in processing times for submissions, according to how they arrive at the agency. Use of the ESG can enable both the earlier arrival of a submission at FDA, and the more rapid completion of the initial FDA processing steps.

Typical time from FDA receipt of submission to dossier available at reviewers’ desks:

- Paper Only: 16 hours
- Paper and Electronic: 16 hours
- eCTD on digital media: 8 hours
- eCTD with non-fillable forms via the ESG: 4 hours
- eCTD with fillable forms via the ESG: 2 hours

Small amendments and supplements, under ideal circumstances, can be available for review within as little as 15 minutes.

These examples illustrate a newly-emerging benefit for eCTD, especially when submitted through the ESG with fillable forms: faster arrival at the reviewer's desk.

*Commentary: The eCTD, when combined with the ESG, can truly offer value for the sponsor in terms of speeding content to reviewers.*

### FDA on Electronic Drug Listing and Drug Establishment Registration

Some context was provided for the new requirements for electronic submission of drug listing and drug establishment information that take effect June 1, 2009. Requirements are driven by need to connect product information with labeling information. Use of Structured Product Labeling (SPL) for labeling and drug listing/drug establishment information allows:

- People-friendly: better readability and access
- Computer-friendly: computer can "find" specific section of the labeling and specific elements within labeling and listing sections
- Information system-friendly: Information in computer readable form which can be imported into information systems. FDA uses extracted data for drug establishment and drug listing
- Publicly available: content of labeling available on DailyMed; drug listing and establishment registration information through NDC directory

Note, the new requirements mandate the use of the SPL-R4 format for these electronic files, *and* the submission of these through the FDA ESG.

*Commentary: This deadline is approaching rapidly and sponsors are advised to plan now and arrange for their electronic solution to be in place in ample time to ensure that listings and registrations can be properly submitted and maintained.*

### FDA Project Manager's Perspective on the Value of eCTD

Key points:

- eCTD submissions facilitate efficient management of applications
- Quality of the submissions is critical to good project management
- Early and frequent communication with FDA is key to providing quality eCTD submissions

Consequences of a flawed electronic submission

- Delayed action
- "Complete Response" action with multiple review cycles

Consequences of a quality electronic submission

- Action by PDUFA date

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- More likely to reach approval in a single review cycle
- The Agency can make a sound decision based on a complete review of the data

*Commentary: While eCTD submissions may not have different PDUFA dates than paper applications, eCTDs are clearly more easily reviewed and more easily managed.*

### FDA eCTD Validation

FDA has updated their review tool to GlobalSubmit Validate 5 which will enable them to provide some eCTD validation reporting back to Sponsors/Applicants.

*Commentary: It is possible that we will see a reduced tolerance from FDA for eCTD validation errors.*

### FDA Top eCTD Validation Issues:

Causes of rejected eCTDs:

- duplicate submissions
- us-regional.xml / form mismatch
- us-regional.xml cannot be read / nonstandard
- eCTD submission sent to the wrong Center
- portions sent outside the eCTD (extra Folders)
- empty folder
- bad characters in file or folder names
- missing Module 1
- incorrect application (6 digits) and sequence (4 digits) numbers

Additional considerations:

- Module 2 must contain relevant, targeted links to Modules 4 and 5
- Module 2 should not contain data, nor thousands of pages
- Study information in Modules 4 and 5 must be accompanied by Study Tagging Files (STFs)
- Modules 4 and 5 should be prepared from the current STF stylesheet and specification

*Commentary: The continued existence of these types of issues underlines the need for very careful approaches to the preparation and QA/QC processes associated with eCTDs.*

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