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*In the next issue of  
**EDC Today:***

eCTD Vendors and  
Their Offerings

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## **An eCTD Primer**

EDC Today is an independent publication on current information and issues in Electronic Clinical Systems (ECS) strategies and technologies for the Biotechnology and Pharmaceutical (Biopharma) industry. Each month we examine topics related to ECS theory, technology, practice, or implementation.

EDC Management has recently been involved in a number of discussions concerning electronic Common Technical Documents (eCTD) and how they are used in an electronic submission, an activity also known as product registration. In our discussions we have come to realize there is a lot of confusion about eCTD, and the submissions process in general. Part of the confusion can be attributed to the FDA accepting both old-style NDA submissions and eCTD submissions, and there are subtle differences between the two.

In this issue, we present a primer on eCTD, attempting to explain what it is and its major components. Our intention is not to delve into the underlying technical details such as eXtensible Markup Language (XML) or Clinical Data Interchange Standards Committee (CDISC) Submission Data Standards Team (SDTM), but rather to highlight the sections that make up eCTD, and the process by which eCTD can be built. Our hope is that companies will assemble the eCTD as studies are being conducted, rather than waiting and having a massive authoring and compilation effort just prior to the actual product submission.

### **Introduction**

The intent of using an eCTD is to create the core of a submission application that can be used for multiple Regulatory Bodies. Furthermore, there is a continuing move to have future submissions be completely and totally electronic and in standardized form. It is intended that future submissions be assessed by Regulatory Bodies' reviewers via ordinary workstations using standardized (and generic) networked applications.

One possibly unexpected benefit of eCTD will be the ability to begin the effort of creating a submission much earlier in the drug development process, thereby extending the timeline and spreading the effort of what has traditionally been a very large and intense activity.

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The eCTD is the work of the International Conference on Harmonisation (ICH) which is administered by a Secretariat based in Geneva, Switzerland. The FDA has been adopting many of the ICH efforts with the realization that common regulations and licensing applications would benefit pharmaceutical and biotechnology companies.

We will begin by presenting some background on the ICH and what the ICH hopes to accomplish, and then outline and describe the contents of an eCTD. We will then describe software tools that are intended to help in the compilation of eCTD and point out that software tools remove the need to understand and work with XML directly. Finally we will summarize all of this and describe how an incremental building of eCTD can make the process of creating and managing a submission easier.

## **Introduction to the International Conference on Harmonisation (ICH)**

The full title of the ICH is the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. The ICH is a unique project bringing together the regulatory authorities of Europe, Japan and the United States and experts from the pharmaceutical industry in the three regions to discuss scientific and technical aspects of product registration.<sup>1</sup>

According to the ICH, their mission is:

- To maintain a forum for a constructive dialogue between regulatory authorities and the pharmaceutical industry on the real and perceived differences in the technical requirements for product registration in the EU, USA and Japan in order to ensure a more timely introduction of new medicinal products, and their availability to patients;
- To contribute to the protection of public health from an international perspective;
- To monitor and update harmonised technical requirements leading to a greater mutual acceptance of research and development data;
- To avoid divergent future requirements through harmonisation of selected topics needed as a result of therapeutic advances and the development of new technologies for the production of medicinal products;
- To facilitate the adoption of new or improved technical research and development approaches which update or replace current practices, where these permit a more economical use of human, animal and material resources, without compromising safety;
- To facilitate the dissemination and communication of information on harmonised guidelines and their use such as to encourage the implementation and integration of common standards<sup>2</sup>

In the United States, applicants creating applications for human pharmaceutical products and related submissions, including abbreviated new drug applications (ANDAs), biologics license applications (BLAs), investigational new drug applications (INDs), new drug applications (NDAs), master files (e.g., drug master files), advertising material, and promotional labeling, are currently expected (but not yet required) to have begun making regulatory submissions to the FDA in electronic format using the electronic common technical document (eCTD) specifications.

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## **What is an eCTD?**

According to the ICH, electronic submission documents should be organized based on the five modules in the eCTD:

### ***Module 1: Administrative Information and Prescribing Information***

This module should contain documents specific to each region; for example, application forms or the proposed label for use in the region. The content and format of this module can be specified by the relevant regulatory authorities and will typically contain:

- Table of Contents of the Submission including Module 1
- Documents Specific to Each Region (for example, application forms, prescribing information)

### ***Module 2: Common Technical Document Summaries***

This module should begin with a general introduction to the pharmaceutical, including its pharmacologic class, mode of action, and proposed clinical use, and should contain the following seven sections in this order:

- CTD Table of Contents
- CTD Introduction
- Quality Overall Summary
- Nonclinical Overview
- Clinical Overview
- Nonclinical Written and Tabulated Summaries
  - o Pharmacology
  - o Pharmacokinetics
  - o Toxicology
- Clinical Summary
  - o Biopharmaceutical Studies and Associated Analytical Methods
  - o Clinical Pharmacology Studies
  - o Clinical Efficacy
  - o Clinical Safety
  - o Literature References
  - o Synopses of Individual Studies

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### ***Module 3: Quality***

This section consists of Chemistry, Manufacturing and Controls (CMC) information:

- Table of Contents of Module 3
- Body of Data
- Literature References

### ***Module 4: Nonclinical Study Reports***

This section consists of pharmacology, pharmacokinetics and toxicology information:

- Table of Contents of Module 4
- Study Reports
- Literature References

### ***Module 5: Clinical Study Reports***

This section consists of the human study reports and related information:

- Table of Contents of Module 5
- Tabular Listing of All Clinical Studies
- Clinical Study Reports
- Literature References

For submissions in the United States, under FDA regulation (21 CFR 11.2(b)(2)), applicants and sponsors are expected to contact the FDA for details on how to proceed with electronic submissions. The FDA fully supports the use of the eCTD backbone files developed through the ICH is expected to facilitate efficient submission handling.

#### **According to the FDA:**

Submissions are a collection of documents. A document is a collection of information that includes forms, reports, and datasets. When making an electronic submission, each document should be provided as a separate file.<sup>3</sup>



## Software That Might Help

Submission documents are complicated, lengthy, and cumbersome. They also require huge expenditures in terms of person-hours to create, proof, validate and publish.

Vendors are stepping in to fill the niche and most offerings are maturing. Like the eCTD specification itself, their offerings are subject to change. However, in general terms, most of the vendors that offer eCTD applications are offering suites of eCTD applications, typically separate programs or modules for the creation, validation, viewing, and archival of eCTD submissions. This software is expected to make the complexity of eCTD processing more manageable for users, as well as being flexible enough to readily adapt to new or revised eCTD initiatives.

eCTD software suite members usually includes an eCTD viewer. A viewer should provide ease of use, simple and straight-forward navigation and intuitive document lifecycle indicators, as well as multi-document viewing and convenient batch printing.

Another suite member will be some sort of eCTD validation software that will automate the tedious process of verifying eCTD submissions. It should make sure submissions are compliant with ICH and regional eCTD specifications, guidance, and industry best practices.

A publishing module will be another common suite member. It should take the complexity of the eCTD specifications out of the assembly and compiling process. Many of the current vendor offerings have simple drag-and-drop operations that allow the user to build eCTD submissions within the application and do so fairly quickly. No specialized eCTD or XML knowledge should be required of the user.

Lastly, there is normally some form of a document management system upon which a Submissions Archive is built. It will be necessary to have a document retrieval solution that supports the controlled retrieval of all or part of a submission. This system will need to be 21 CFR Part 11 compliant and should provide search tools and swift access to submission documents for use in the event of auditing or litigation.

With the advent of eCTD, the lifecycle of a document isn't final after submission. Reference to a document and lifecycle operations (e.g., annual updates) may occur at any time.

## Conclusion

In the past, a marketing submission (product license application) has been largely done in bulk immediately after a phase III pivotal trial. eCTD promises to spread the large effort required to generate/create a submission package over the total life of the drug/product development effort.

EDC Management's experience with submissions has shown us that typically a massive effort is put forth by many people just prior to the filing of a submission. Document management systems are a start for making the daunting tasks of submissions more manageable. With the maturation of the eCTD software packages and document management, EDC Management sees the day where as each study is completed, all the components of the study that become part of either Module 4 or Module 5 (depending upon whether the study is pre-clinical or clinical), can be quickly built and finalized.

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Likewise, Module 3 on Quality can be built as the chemical and manufacturing processes are designed and stabilized.

EDC Management realizes that Module 2 will still need to be put together towards the end of the process of creating the eCTD assembly since it contains summaries of individual study results. It is thought, however, that the size and intensity of this effort can be made more manageable.

EDC Management applauds the efforts of the ICH as it strives to ensure timelier introduction of new medicinal products and their availability to patients by reducing the burden on pharmaceutical companies filing product license applications. EDC Management looks forward to better defined processes and streamlined regulations.

#### Resources

<sup>1</sup> <http://www.ich.org>

<sup>2</sup> <http://www.ich.org/cache/html/581-272-1.html>

<sup>3</sup> <http://www.fda.gov/cder/guidance/7087rev2.pdf>



## Who's behind the research?

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Our lead researcher, Kirk Mousley, PhD received BS and MS degrees in Electrical Engineering from MIT and a PhD in Computer Science from Lehigh University. He has been the President of Mousley Consulting, Inc. since its founding in 1993 and has directed the company's efforts in the areas of clinical database design, data editing/cleaning, document management, and submissions.

Karl Mousley received his BS in Mechanical Engineering from Rose-Hulman Institute of Technology and a MS in Computer Science from Villanova University. He has been a senior member of the technical staff at Mousley Consulting, Inc. since 1993. Among his significant accomplishments are the investigation, evaluation, and implementation of new computer technologies for clinical data management systems and developing strategic plans for integrating these technologies into current systems. He has extensive experience preparing Standard Operating Procedures (SOPs).



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