

Fall

FrontLine

2005

eClinical Research and Development

THE FDA: A Year of Challenges and Changes

In This Issue:

**Electronic Labeling Initiatives
From Document Management to Submission Management
The eCTD Guidance for Industry is Finally FINAL!
Keep Your Eyes on the EU!**

In This Issue:



THE FDA: A Year of Challenges and Changes

Electronic Labeling Initiatives

From Document Management to Submission Management

The eCTD Guidance for Industry is Finally FINAL!

Keep Your Eyes on the EU!

As the year draws to a close, many industry professionals are ramping up to prepare for the "end-of-the-year submission crunch time". The team at Octagon is doing the same. As our submission teams move forward in their compilation, review and delivery cycles, there is one tool of the trade that we utilize to keep multi-disciplinary teams focused on meeting submission deadlines. This fundamental tool is a submission content plan. A thorough and complete content plan is a critical driver in submission activities. It provides a roadmap of submission components, resources and expected delivery dates and often acts as a catalyst for coordination of submission activities across multiple functions. Even as the plan changes, it offers a baseline perspective that helps delivery teams develop resource strategies and track statuses of all expected components from creation to completion. The upfront planning and identification of components is usually difficult, tedious and requires input from multiple functional areas. However, a complete plan alleviates last minute resourcing bottlenecks and enables submission managers to consider multiple options when issues do arise. Most importantly, the plan minimizes the risk of missing a submission date. As you prepare for "submission season", invest time and effort into the content plan now and you won't regret it later.

Octagon Introduces StartingPoint™ 2.0

StartingPoint 2.0 template package continues Octagon's commitment to simplify the submission authoring process and speed up electronic publishing processes.

- The latest version includes support for auto numbered heading styles, which facilitates author cross-referencing tasks.
- Toolbar enhancements include quick access buttons for commonly used tasks such as inserting captions, cross-references and additional symbols.
- Copying and pasting have been improved through a toolbar button that enables users to copy and paste unformatted text, eliminating the introduction of unsupported or error prone styles into a templated document.

Please contact us for a demo or if you need more information.

Join Octagon at the following conferences:

Drug Information Association Conference: 19th Annual Electronic Document Management Meeting and Exhibition
February 7-9, 2006
Philadelphia Marriott Downtown
Philadelphia, PA

Drug Information Association Conference: 18th Annual EuroMeeting
March 6-8, 2006
Le Palais des congrès
Paris, France

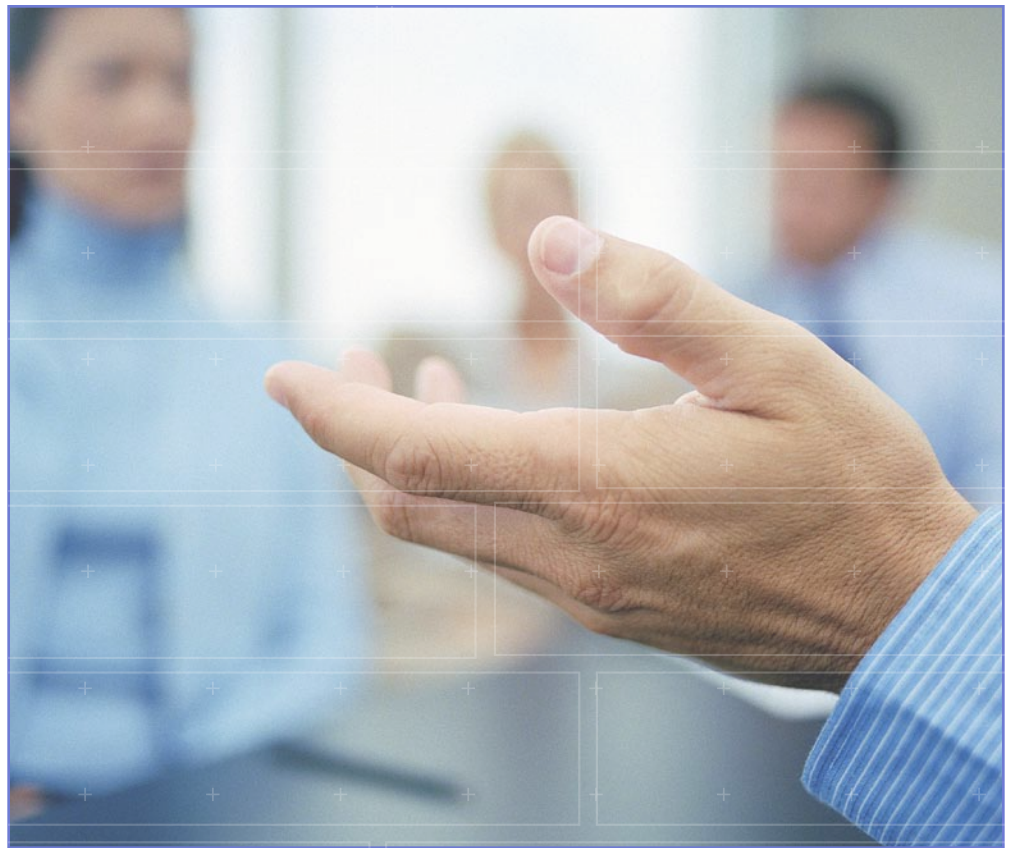
Drug Information Association Conference: 21st Annual Clinical Data Management Symposium and Exhibition
March 26-28, 2006
Philadelphia Marriott Downtown
Philadelphia, PA

THE FDA: A Year of challenges and Changes

Jann Kochel
Senior Regulatory
Project Manager

Katie Russo
Regulatory Affairs Associate

With the year coming to a close, people often take a moment to consider where they have been, what they have done over the last 12 months and what changes have taken place within “their world”. Here at Octagon, a large part of our world is the FDA. Looking back, we see that the FDA is not a static government agency. Over the past year, the FDA has been confronted with many challenges. Granted, there will always be obstacles while protecting the public’s welfare, but the serious safety issues that have lead to the withdrawal of some of the COX-2 inhibitors have made this even more difficult. The FDA is also facing the challenge of being able to provide drugs to the market for unmet medical needs in a timely manner. The agency has always had a competent drug development and post-marketing safety program, but over the past year, FDA has been striving for even more efficiency. The following are a few examples of the programs the FDA is implementing to provide consumers and healthcare professionals with the most accurate biopharmaceutical information, to assist pharmaceutical companies in developing much needed drugs and to help ensure their review procedures expedite the process of getting new drugs to the market.



The first priority is to ensure the public’s safety by providing information on drug risks and benefits to healthcare professionals and patients. In the past,



the primary mechanism for this communication was through the dissemination of the package insert. However, the package insert is not always up-to-date and does not always make it past the pharmacy shelf. When a revision is made, it may take months for the new information to make it to the public, including the physicians responsible for safely prescribing the medication. In order to eliminate the delay, the agency has begun to execute many changes. A few of these modifications include Structured Product Labeling (SPL) and Drug Watch databases.

On October 31, 2005, SPL became effective with the FDA mandate that all approved package inserts be submitted in XML format. This enables all physicians, pharmacists and consumers to access to the most current package insert through the National Library of Medicine’s data-

base. (For more specific details, please refer to the SPL article in this issue.) The agency also published a draft guideline entitled, “FDA’s ‘Drug Watch’ for Emerging Drug Safety Information,” dated May 2005. The purpose of Drug Watch is to identify the drugs for which the FDA is actively evaluating early safety signals. All interested parties can access this information via the FDA’s web page. The goal of both SPL and Drug Watch is to distribute important and timely safety information for marketed products.

The FDA is not only concentrating their efforts to the public sector; they are also focusing on the business sector in order to expedite getting novel drugs to the market. The FDA and the pharmaceutical industry agree that the drug development process is currently riddled with roadblocks. Currently, the guidance documents created by the FDA are intended to give sponsors insight into best practices on a variety of topics within the drug development process in order to promote consistency and efficiency across the industry. However, it seems that even more interaction between the FDA and the sponsor could

improve the quality of marketing applications. Two current initiatives are the Continuous Marketing Application (CMA) and Exploratory IND studies.

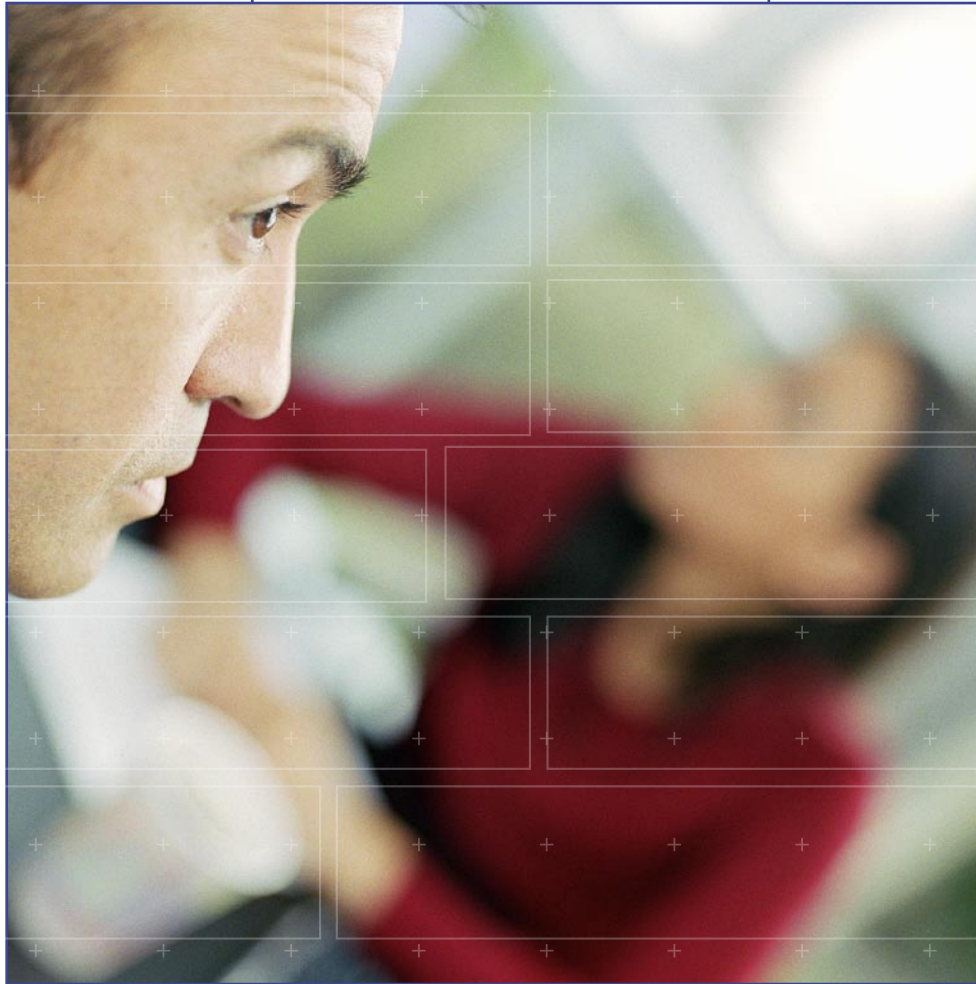
The basis behind the CMA is to provide the sponsor feedback prior to the review of the complete submission. This program is currently available for NDAs

as well as those that will fail. Having this information may prevent sponsors from utilizing resources for products with no promise of making it to market. Further details can be located in the FDA’s “Guidance for Industry Continuous Marketing Application: Pilot 2 - Scientific Feedback and Interactions During Development of Fast Track Products Under PDUFA.”

The initiative that has been put forth by the FDA to promote efficiency in the drug development process is the option of exploratory human IND studies. The draft guidance document, “Guidance for Industry, Investigators and Reviewers Exploratory IND Studies,” provides the details regarding such studies, as well as the non-clinical requirements needed to begin these trials. These studies are very early Phase I trials where the subject receives

a sub-therapeutic dose of drug with very limited exposure. The goal of these studies should be a pharmacological endpoint, not tolerability. The agency hopes that this option will help to quickly discover the candidate products that have the most promise in humans, as well as prevent sponsors from expending unnecessary resources on a new chemical entity that has

that have obtained priority review. However, earlier this year, the FDA expanded the CMA pilot to apply to the IND phase for Fast Track drugs. The sponsor and the agency agree upon the form and frequency of feedback at the beginning of the process. Receiving feedback during the IND phase can help to identify the drug products that will be most successful in clinical trials



little potential. It is also possible for these studies to help limit the total number of human subjects required for clinical studies.

Not all of the FDA steps towards a more efficient process are directly related to the consumer, healthcare professional, or the sponsor. For instance, the FDA has incorporated the electronic common technical document (eCTD) as an acceptable electronic submission format. The eCTD removes redundancy in the review process by utilizing a format that allows the sponsor to build on the submission. Therefore, not only does information not have to be submitted more than once, but specific pieces can also be updated. This concept may accelerate the review process because FDA reviewers can quickly identify updated components and do not have to waste time re-evaluating the information that was previously submitted and reviewed. Currently, the FDA has accepted approximately 26 IND and 45 NDA original applications in eCTD format. An additional change regarding electronic submissions

pertains to refuse to files (RTFs). For the first time, the agency is issuing RTFs for lack of electronic navigational components. The FDA is requiring a good quality submission (with adequate hyperlinks and bookmarks) so that the review process can be completed in a timely manner. Another move to increase agency performance is the consolidation of CDER's personnel. At the end of the summer, CDER began its move to a new facility at White Oaks. In this new facility, all the review divisions will be under one roof, thus decreasing communication obstacles.

In a short amount of time, the FDA has had many hurdles to jump. They had many questions to answer pertaining to the safety debacle surrounding the COX-2 inhibitors while simultaneously assuring the public that programs are being implemented to help avoid a future safety crisis. However, the FDA cannot solely focus on the safety of existing products. There are many patients who desperately need new life saving drugs, which requires the agency and sponsors to work closely together in order to achieve this goal. The agency real-

izes that efficiency must begin with a well-designed review process that decreases redundancies. Even though there have been significant challenges, the FDA continues to respond in a positive manner with new initiatives that will help to overcome the existing inefficiencies throughout the drug development process.

Electronic Labeling Initiatives

*Patrick Thomas
Senior Regulatory
Project Manager*

In the fourth quarter of 2005, two significant XML-based initiatives are becoming reality for the pharmaceutical/biotechnology industry: SPL (Structured Product Labeling) in the United States and PIM (Product Information Management) in the European Union (EU). While both of the standards handle product information and are based on XML (Extensible Markup Language), they are very different in a number of ways.

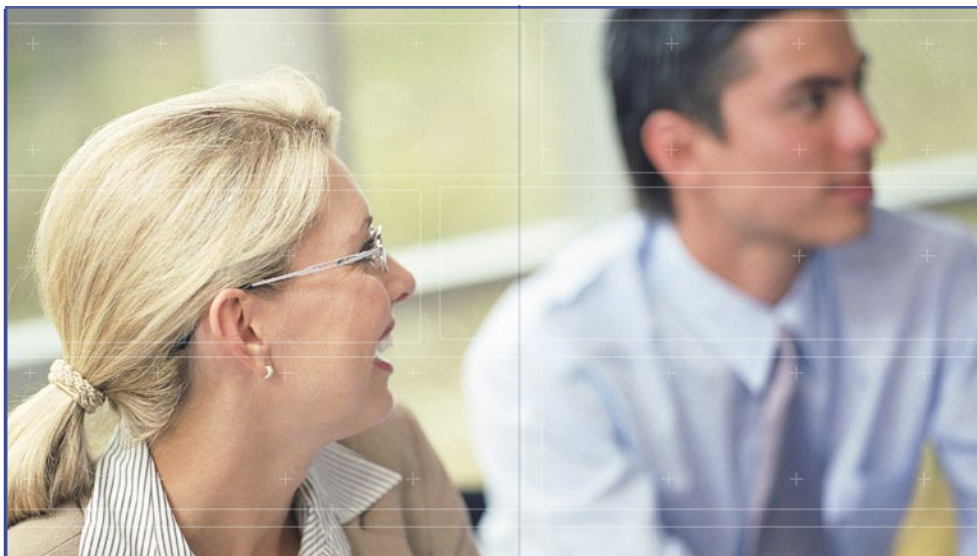


SPL (Structured Product Labeling)

Since June 8, 2004, the submission of the 'content of labeling' in electronic format in support of New Drug Applications (NDA), Abbreviated New Drug Applications (ANDA), supplements, and annual reports has been mandatory. The 'content of labeling', is defined as "the contents of the package insert or professional labeling, including all text, tables, and figures". Up until October 31 of this year, compliance with the 'electronic labeling rule' could be achieved through the submission of the content of labeling in either PDF or XML (SPL) format. On October 31, however, SPL became the only acceptable format for the submission of the content of labeling in electronic format for prescription drug products.

SPL Release 2 is an HL7 (Health Level Seven) standard for the electronic exchange of product labeling information. FDA has adopted a subset of this standard, Release 2a, for implementation and is expected to implement the full Release 2 following the finalization of the Physician's Labeling Rule.

SPL is part of the DailyMed Initiative, a collaboration between FDA, National Library of Medicine (NLM), the pharmaceutical/biotechnology industry, and healthcare information providers. The goal of the initiative is to "Enhance patient safety through accessible medication information". In order to support this goal, the National Library of Medicine is hosting an online database, called DailyMed (<http://dailymed.nlm.nih.gov/dailymed/>). The database, which is free and available to anyone



with internet access, provides a consistent source of the most up to date prescription drug product information available. Future phases of this initiative will expand SPL to cover vaccines, over-the-counter products, veterinary medicines, and medical devices.

There are a number of key FDA documents and files pertaining to SPL, all of which can be found on the FDA's 'Structured Product Labeling Resources' web page (<http://www.fda.gov/oc/data-council/spl.html>). Among the documents are guidelines for creating SPL, "SPL Implementation Guide for FDA Content of Labeling Submissions - Release 2a" and submitting SPL, "Guidance for Industry: Providing Regulatory Submissions in Electronic Format - Content of Labeling".

PIM (Product Information Management)

In the European Union, a separate XML-based electronic labeling initiative, PIM or Product Information Management, is approaching reality with an implementation date of November 25, 2005: The PIM initiative is a collaboration between the European Medicines Evaluation Agency

(EMA), National competent authorities, and the European Federation of Pharmaceutical Industries and Associations (EFPIA). The initiative's goal is to provide an efficient way of handling product information for the registration of human medicines via the Centralised Procedure. This is accomplished through the PIM Data Exchange Standard (DES), an XML specification that allows sponsors utilizing the Centralised Procedure to submit all product information documents relating to a marketing application in a single XML file. It is important to note, however, that, unlike SPL, PIM submissions are optional, though highly encouraged by the EMA. Future phases of the PIM initiative will entail an expansion of scope to cover applications filed via the Mutual Recognition/Decentralised and National Procedures.

Unlike SPL, which only represents the 'content of labeling', PIM covers all of the product information documents that are submitting with a marketing application in the EU including the SPC (Summary of Product Characteristics), Annex II (Conditions of the Marketing Authori-

sation), Labelling, the Package Leaflet, as well as all required linguistic versions of these documents. Another key difference between the standards is that the PIM standard supports a transactional model which facilitates exchange of comments during the review between the regulators and the application sponsor, while SPL is currently limited to a one-way (sponsor to FDA) transfer of product information.

As part of an EMEA initiative to provide business-assistance for small- to medium sized organizations, the Agency is providing a free tool for the creation and management of PIM submissions. Called the Light Authoring Tool (LAT), the application will allow sponsors to "...build XML-based product information using an interface that will provide viewing, editing and life-cycle management (LCM) capabilities". The tool as well as important documentation and information regarding the PIM initiative can be downloaded from the EMEA PIM website (<http://pim.emea.eu.int/>).

In conclusion, the new XML-based initiatives that have been described are important steps forward in the realm of electronic-only submissions for product registration. Both standards are going to force pharmaceutical/ biotechnology sponsors to evaluate their internal processes and perhaps modify their outlook towards electronic submissions. For those organizations that to this point have dealt only in paper applications, this may represent a favorable time to begin moving towards an electronic-only submission environment.

From Document Management to Submission Management

*Gareth Williams
Principal Consultant I,
Process Solutions*

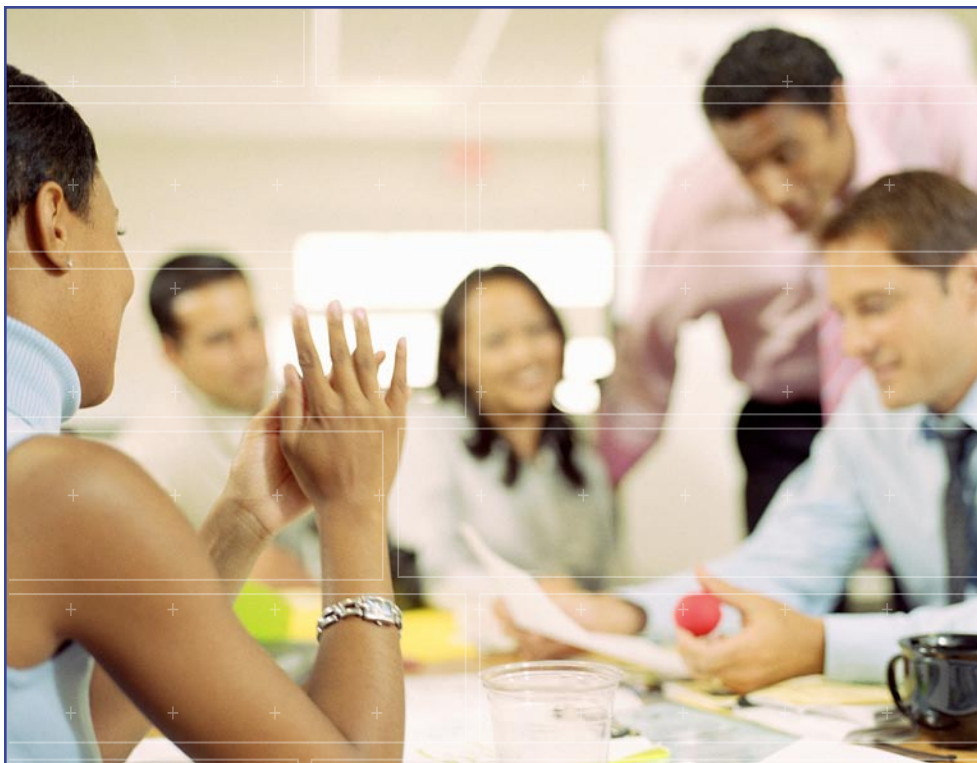
The regulatory landscape continues to change at a furious pace. In times past, Regulatory Operations assembled the vast majority of documents submitted to agencies for approval. Functional areas typically threw documents over the proverbial wall for RO specialists to re-format to meet agency standards. For over a decade, electronic document management systems (EDMS) such as EMC's Documentum have played a crucial role in helping regulatory professionals manage these documents. More recently, many companies have sought to maximize their investment in EDMS by spreading

the technology beyond Regulatory Affairs, taking advantage of evolving functionality (such as workflow and virtual documents) to facilitate more effective collaboration between authors and reviewers. These groups are often spread widely across different departments and geographical locations. Publishing has also become a critical component of the overall document management environment, as agencies' affinity for electronic submissions have grown. Then along came eCTD: the industry initiative sponsored by the International Conference on Harmonization (ICH). The eCTD is an electronic submission format that includes PDF and SAS "transport files" in a specified file/folder structure with an XML backbone, which provides navigation across these files.

eCTD has led to a fundamental shift in the drug submission world. Lifecycle management is at the center of the eCTD specification, where relationships exist between components of a submission and previously submitted information. Managing these components, small chunks (or 'granules') of the old-world 'document', is the focus of submission management. Produced by multiple authors spread across multiple functions, each component has a 'life' of its own and must be managed accordingly. For maximum leverage of new agency guidance on electronic submissions, components must be written only once, yet used multiple times. This requires robust processes and systems to track the lifecycle of each component.

So what's the big deal? Isn't submission management just document management re-badged? To be sure, there are many technical





similarities between the two: for example, components and documents alike require authoring and publishing tools, version management and document attributes. There are also many challenges common to both document and submission management: challenges which may differ in complexity and scope, but which are fundamentally the same. For example, laborious hand pagination gave way to electronic bookmarks and hyperlinks. With the eCTD, providing navigation and utilizing review tools is essential, but is in order of magnitude more difficult. Quality control is more vital than ever, with submission attributes, module attributes, document type definitions (DTDs) and the like to contend with. Likewise, standards which have long been critical to effective automated submission production, have assumed a wider scope and influence. Submission and file level metadata are no longer merely helpful 'hooks' for internal

search tools, but rather an integral component of an official eCTD submission. Tracking and management of this metadata has never been more important. The 'pursuit of perfection' poses another significant challenge: once a laudable goal in the hard copy and electronic document world, near perfection is virtually an imperative in the eCTD world. The odd erroneous character or symbol could be tolerated prior to the eCTD, but something as seemingly innocuous as a capital letter out of place can lead to an eCTD not validating at the FDA. And what of the differences? Traditional EDMS tools are document-centric, and optimized for managing large compound documents. In contrast, submission management is more process-centric and focuses on individual submission components - in other words, much smaller documents. EDMS typically don't manage the submission process, either - MS project plans and Excel spread-

sheets are often found in abundance. A good submission management system, on the other hand, provides dynamic, real-time management of processes, issues and critical activities. So what does this all mean for you? If you already have an EDMS in place, what impact will moving to eCTD have? How flexible is the system to respond to the changing processes the new eCTD world will demand? Do you need a new system altogether? And what if you don't yet have an EDMS in place? Before rushing out to buy one, what criteria should you use to evaluate available solutions? How can you be sure the system will support the processes you need, instead of requiring you to 'shoe-horn' your processes to fit the system? Will the system be able to handle the challenges of component-level authoring, version control and review, together with resource management and submission planning? Whatever your current situation, a critical first step must be to thoroughly review your e-submission readiness. The review should cover all functional areas and address everything from staff awareness of eSub specifications and resource needs to defining critical processes and the system(s) that will be required to support them. Based on known submission timelines, corporate strategy and resourcing requirements, develop a 'Roadmap' that highlights key decision points on the road to becoming eSub-ready. Effective adoption of the eCTD requires that each functional area must be educated on, and understand, eSub deliverables.

Reductions in rework and the elimination of redundancy will follow, with gaps between the functions closing and processes being optimized.

eCTD is here to stay - your final destination is not open to question. Start planning your journey now, and navigate your way to effective submission management.



ATTENTION eCTD WATCHERS - The eCTD Guidance for Industry is finally FINAL!

*Nancy Smerkanich
Vice President,
Regulatory Affairs*

Officially titled "Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related

Submissions Using the eCTD Specifications," this document differs very little from the draft that was originally issued in Aug 2003. Of note however are the following:

1. The agency has included eCTD in the title (it's the little things that count).
2. On p. 4 there is a mention that "In time, the other guidances may be withdrawn because they are no longer needed". We know this is applicable to OGD which has stated publicly that they wish to withdraw the eANDA guidance, but we also suspect it refers to the CBER eIND guidance and perhaps the old eNDA guidance as well.
3. On p.5 there is some confusing verbiage about the need to reference in the text prior submissions including application number, submission dates, etc. It should be noted that for M2-5 documents this limits their reuse and repurposing. In the next paragraph there is a statement about the utility of resubmitting documents that were non-eCTD.
4. On p. 8 there is a statement within the pdf bookmarking and hypertext links section that states "...some documents may be subsequently replaced or appended, possibly rendering the link obsolete, so linking should be used cautiously." In follow-up discussions with FDA, Ken Edmunds indicated that the agency is dealing with the "linking problem" in a two step process, both of which are tool dependent. The first step will utilize a pop-up message to reviewers indicating that the document has been

superseded and the second will actually "follow" the path to the new file.

What is also noteworthy about this guidance is that it refers to and relies heavily on the DTD and specifications as well as additional guidance.

We anticipate that the agency will be issuing additional guidance on Life-cycle Management for both documents and dossiers now that they have publicly illustrated how to utilize the modified file path to cross reference not only within an eCTD dossier but across eCTDs.

The most recent metrics released by FDA on the number of active eCTD dossiers and the instances/sequences submitted to them is captured below:

	Applications	Submissions
IND	35	184
NDA/BLA	47	628
ANDA	37	109
DMF	5	6
Total	126	934

ATTENTION eCTD WATCHERS - Keep your Eyes on the EU!

*Nancy Smerkanich
Vice President,
Regulatory Affairs*

As most of you have are aware, a number of countries in the EU have announced dates for both e-only submission processes as well as mandatory eCTD. Important dates are as follows:

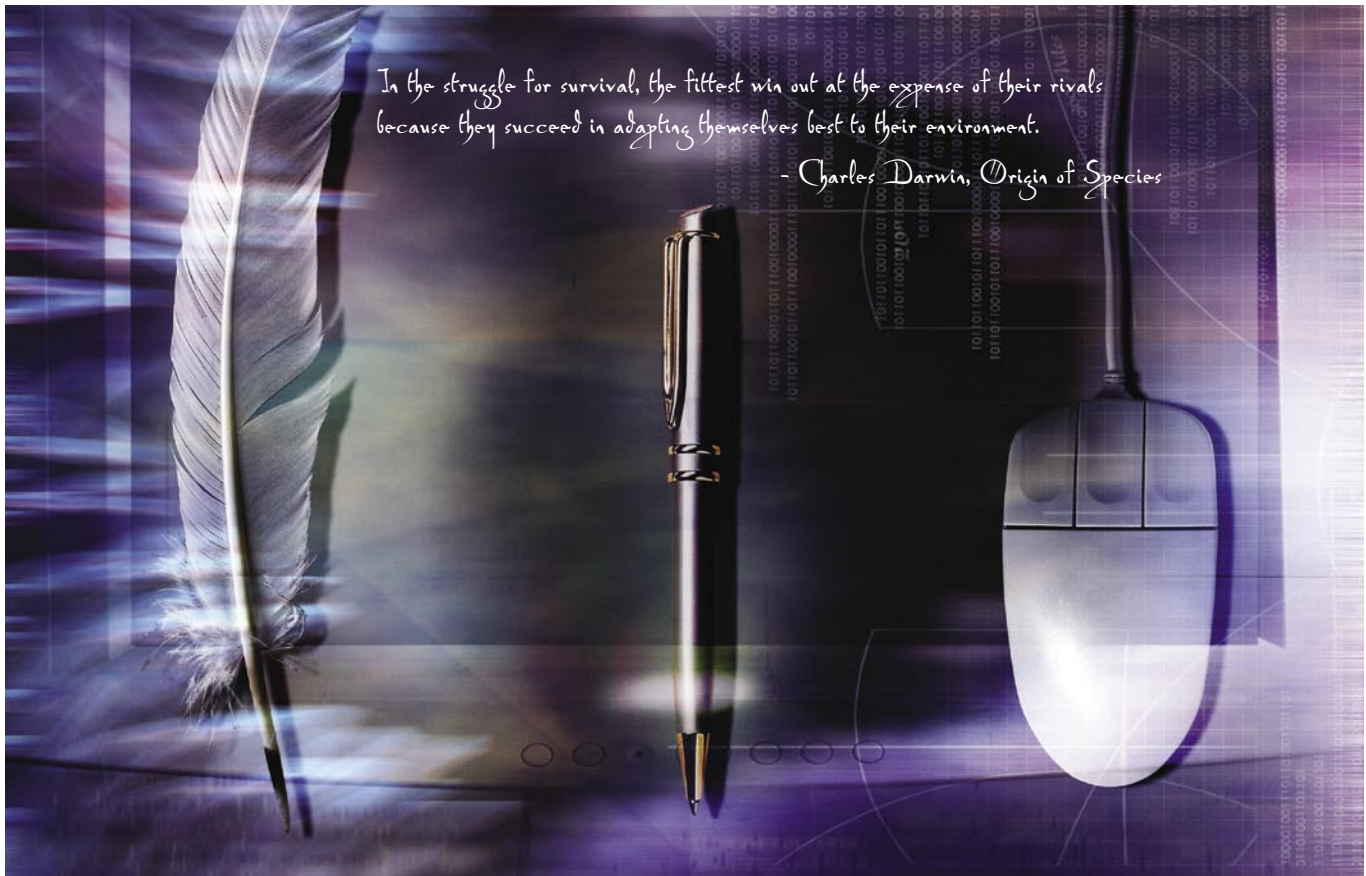
- January 1, 2007 for Belgium and the Netherlands.
- The UK and France are headed in that direction and the EMEA

has announced a back end date of 31 December 31, 2009, provided all member states can

- accept e-only by then.
- In addition, the ICH is including requests for two-way communication as part of eCTD

- implementation in the EU.
- Finally, a revised EU M1 specification will be available in December, 2005.

Darwin isn't the only one who knows about evolution.



Octagon Research Solutions is leading the electronic transformation of clinical R&D. Our clinical data strategy offerings address evolving standards such as CDISC SDTM. We help our clients embrace new standards, uncover new efficiencies and transform business processes.

Our clinical information experts offer:

- CDISC Training
- CDISC Transition Assessments
- Implementation Assistance
- Legacy Conversion Services

Octagon is:

- Primary Trainer for CDISC SDTM for Human Clinical Trials
- CDISC Registered Solutions Provider
- CDISC Corporate Sponsor

Octagon's cross-functional expertise will strengthen your organization to survive and succeed.

eSub Experts
A Process Approach in Everything We Do.

Octagon
Research Solutions, Inc.

585 East Swedesford Road, Suite 200 • Wayne, PA 19087 • Phone: (610) 535-6500 • Fax: (610) 535-6515 • E-mail: info@octagonresearch.com

Regulatory Solutions Clinical Solutions Process Solutions IT Solutions