

Summer

FrontLine

2005

eClinical Research and Development

The Critical Path Conundrum

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What's Up Doc? The Document (R)evolution

Thanks to all of you who visited our exhibit booth at the DIA 41st Annual Meeting in Washington, DC. We enjoyed meeting you and hope to see you at future events.

SPL Webinar Series

Part 2: Implementation Approaches to Structured Product Labeling (SPL)

Date: August 17, 2005

Time: 11:00 am - 12:00 pm EDT

To register, please contact Kathy Bouldin at 610.535.6500, ext. 556 or email kbouldin@octagonresearch.com or register directly on our Website at http://www.octagonresearch.com/webinar_sign_up.html

DIA Structured Product Labeling Conference

August 23-24, 2005

Washington Marriott Hotel
Washington, DC

DIA 6th European Electronic Document Management Conference

September 11-13, 2005

Hotel Sofitel Paris Forum Rive Gauche
Paris, FRANCE

Society for Clinical Data Management 2005 Fall Conference

October 9-11, 2005

Sheraton San Diego Hotel and Marina
San Diego, CA

RAPS Annual Meeting

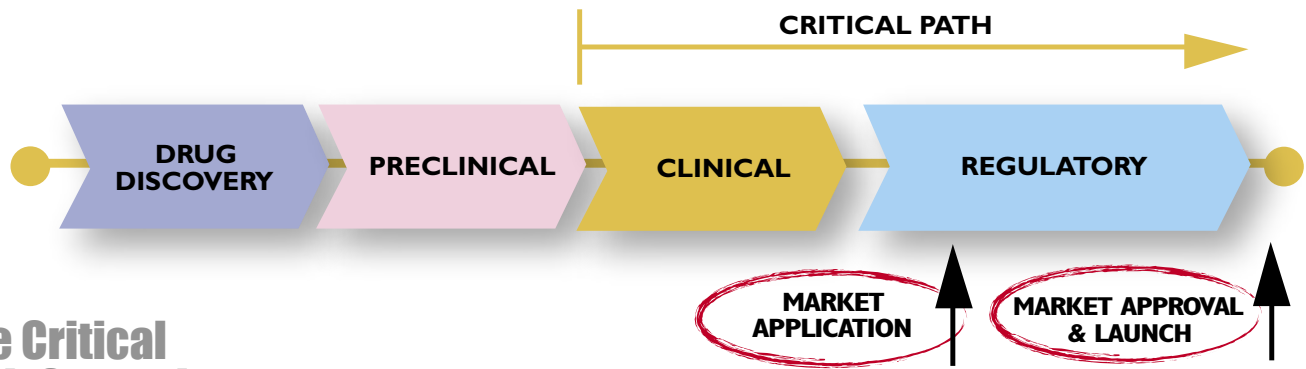
October 16-19, 2005

Baltimore Marriott Waterfront
Baltimore, MD

Co-hosted by:

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The Critical Path Conundrum

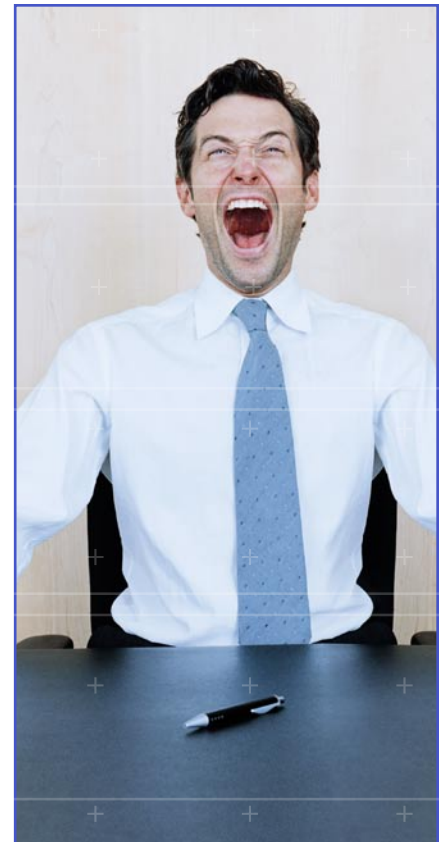
Webster's dictionary defines a conundrum as "a question or problem having only a conjectural answer; an intricate or difficult problem; a mystery." American Heritage Dictionary asserts that a conundrum is "a paradoxical, insoluble, or difficult problem; a dilemma". We all encounter conundrums as we interact with the world, whether in trying to raise our children or manage our careers and lives.

It is clear that the biopharmaceutical industry is in the midst of its own conundrum. Both confounding and enabling is the confluence of four key industry catalysts that will help solve the dilemma: evolving standardization, process synchronization, performance optimization and electronic transformation.

To learn more about the critical path conundrum, please visit our newly designed website

and download The Critical Path Conundrum, a white paper that offers valuable insight into current industry trends and associated issues.

<http://www.octagonresearch.com/pdfs/Processwhitepaper.pdf>



The Past, the Present ... eCTD

Jann Kochel, Senior Regulatory Manager

Submission time for Investigational New Drug Applications (INDs), New Drug Applications (NDAs), and Biological License Applications (BLAs), is always stressful for a pharmaceutical company, especially for the Regulatory Department. One of their critical tasks is to compile an accurate and user-friendly application. Compiling an eCTD for an initial IND application can make memories of years gone by seem pleasant. Submission assembly has always been a quality control nightmare for regulatory professionals, and it appears that

complications will multiply into the future. In the past, perfect submission compilation has always been a goal, but now it is imperative.

Industry standards and FDA expectations for submissions have evolved over the years. First, there was the paper submission, and in 1997, the next generation emerged when the FDA released a draft guideline for submitting Items 11 and 12 electronically to CDER/CBER. Then in 1999 published final guidelines for submitting full electronic NDAs, followed by CBER publishing a guideline in 2002 for submitting electronic INDs, and now there is the electronic Common Technical Document (eCTD). Even though the FDA does not stipulate the format of a submission, they do recommend

electronic submissions.

Technology has slowly made the tedious paper submission almost obsolete. The paper submission consisted of a manual table of contents, and tabs for navigation. The information was divided among volumes that were no more than two-inches thick and continuous submission pagination was applied to all the volumes. Applying this pagination was very laborious as volume after volume was paginated by hand. In electronic submissions, the navigation changed to bookmarks and hyperlinks. There was no more need for volumes or submission pagination or tabs, but this did not eliminate the number of quality checks conducted by Regulatory. There were thousands of bookmarks and hyperlinks that needed verification to ensure proper navigation, as well as technology requirements, such as document information fields.

Then came the quantum leap.

With the eCTD, the same thousand bookmarks and hyperlinks need to be checked, but now document granularity, submission attributes, module attributes, unique IDs, file names, document IDs, document titles, operations, check sums, study tagging files (STFs), document type definitions (DTDs), style sheets, and Extensible Markup Language (XML) backbones are additional concerns. Tables of contents have been replaced by the XML backbone, which do not resemble a typical table of contents; it is now computer code and jargon. Another major change with eCTD is that paper is no longer an alternative. Once a company commits to eCTD, all submissions must be in eCTD format. It



is not an option to sprint to the copy machine and make three copies of an IND safety report and place them in a Federal Express envelope.

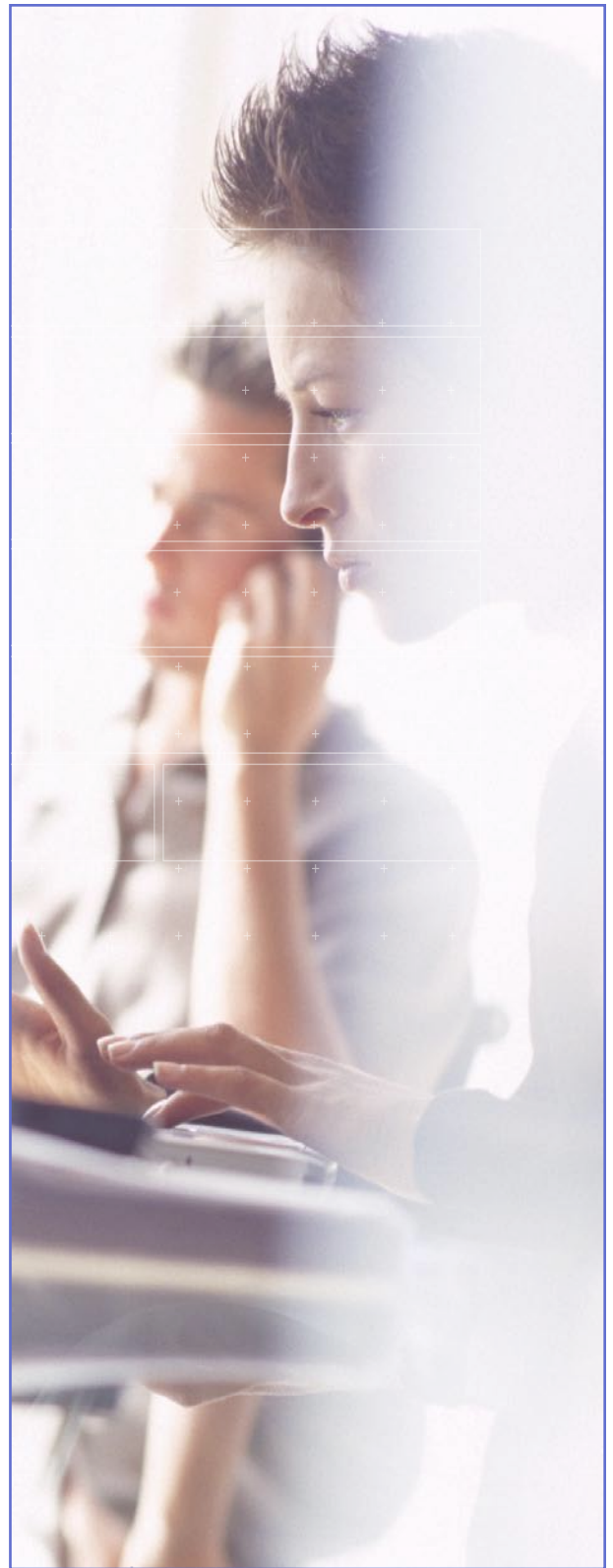
As the submission deadline looms, Regulatory will always have to make decisions during the last minutes. Even though Regulatory always wants to compile an error-free submission, in reality that is generally not the case. Regardless of the numerous QC processes that are in place, as the submission is being packaged, it is not uncommon to find typographical errors on tabs, tables of contents, or in bookmark structures. Then a decision needs to be made æ should the submission be delayed in order to correct the mistake? Nine times out of ten, the answer will be not to delay the submission because the error will not hinder the review of the application. That cannot happen with an eCTD. If one file name contains a capital letter, it will not validate at the FDA; if a backslash is mistakenly used rather than a forward slash, it will not validate at the FDA; if a leading zero is not used in the application number, it will not validate at the FDA.



The list is endless.

The eCTD is creating the need for pharmaceutical companies to acquire additional tools for assisting with the immense task of verifying all submission documents and their associated metadata. Due to complexities of an eCTD submission, traditional quality control processes will not be efficient. There is definitely a need for computer software and validation tools to help assure all the metadata is within the FDA specifications. For example, a software program is much more efficient than an individual armed with spreadsheets at determining if a unique ID has been used for each document or that the check sums are all lower case. However, computer systems cannot determine the accuracy of all the information. The regulatory specialist needs to have a complete understanding of eCTD submissions to ensure all the content, operations, and navigation is correct.

Over the past decade many changes have occurred in submission compilation and organization. Every submission format poses challenges for the regulatory expert. However, the days of the simple paper submission have passed. Before companies make the transition to eCTD, they need to realize the magnitude of the changes and how crucial it is to have an accurate understanding of all the eCTD requirements.



The right tools and processes now must be in place in order to compile the perfect submission.

What's Up Doc? The Document (R)evolution

*Jennifer Jaye, Director,
Process Consulting*

Prior to the electronic era, a document was simply a piece of paper containing text. Today, a document's identity is irretrievably linked to its file type and the technology that created it, and for most authors, that technology is Microsoft Word (Word) and the associated file type is doc.

Most of us in the electronic world understand that an electronic document does not work alone. There are macros and styles operating behind the scenes. You have, no doubt, heard the expression: behind every good man is a good woman (This is a very old expression.)? Nonetheless, the same can be said for an electronic document. Behind every good electronic Word document is a good template.

Most people understand the concept of templates. Nonetheless, there is still a great deal of confusion around their usage.

A doc file type may be used as a "model" document but a true template is distinguished by a dot file type, the most famous being Normal.dot. This is the template that resides in Word and is automatically used whenever you create a new Word document. Click on a dot file and you create an exact replica of the document in a doc format. This is not true for doc documents.

Templates may be blank, like Normal.dot or they may contain text. Blank templates are commonly known as Style Templates. They contain a company's preferred styles, margins and headers and footers, among other things. Templates that contain standard content, including the use of boilerplate text, are known as, Content Templates. The best practice is to create and manage style and content templates separately and merge them, as required.

There are many benefits to using templates. Simply put, they help authors write documents and they do this in several ways. A template separates form from content and allows the author to focus on writing rather than formatting the document. Secondly,

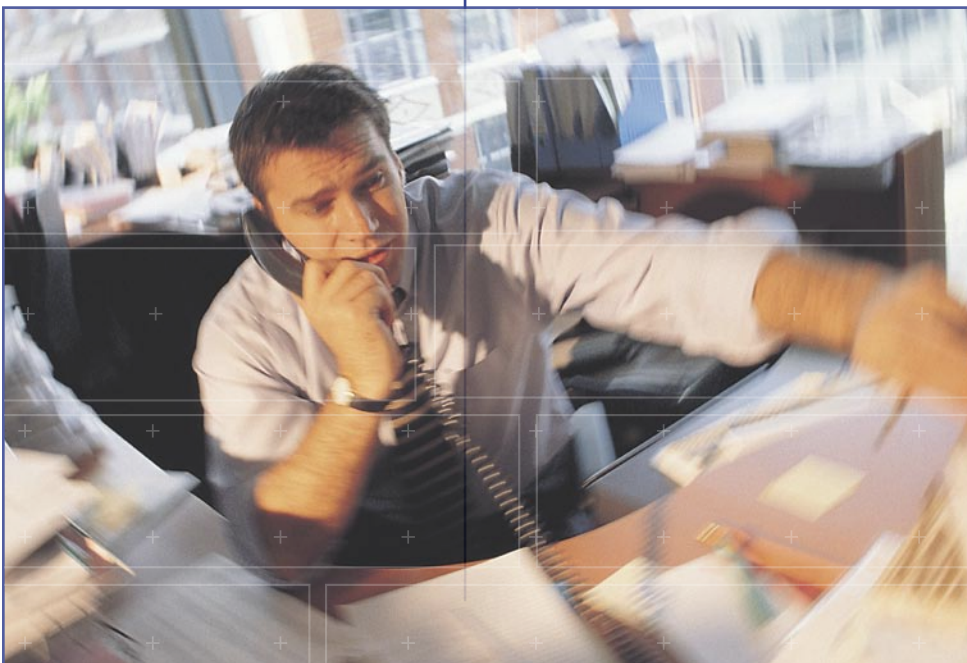
a template provides customization of repetitive tasks such as the application of custom styles, insertion of commonly used symbols, creation of tables and resizing of pages from landscape to portrait. In addition, the template may provide instruction for the author. This is often formatted as "hidden text" and removed when the document is final. This is especially helpful in the pharmaceutical industry where content is governed by numerous guidelines.

But ease of use for authors is not the only reason to use templates. Templates provide a consistent look and feel across documents. This is important when documents are written by different authors and combined into one final submission, as they are in the pharmaceutical industry.

Authors aren't the only beneficiaries of templates. The use of templates facilitates the electronic publishing of documents for submission to regulatory agencies. When heading styles are used consistently throughout a document, most publishing tools can use the heading styles to automatically create the bookmarks required by the FDA guidelines. This clearly expedites the publishing process and reduces the amount of quality assurance that must be performed on the bookmarks.

As for management, templates represent controlling the output to meet industry requirements. Templates go a long way to ensuring that documents will meet regulatory authority guidelines for content and format.

Template usage is not without its problems, however. I have seen poorly designed templates reduce grown men and women to tears. What are the caveats of a good template? A good template will not require the user



to be an MS Word guru. A good template will truly separate the mechanics of writing from the actual writing itself. A good template will ensure authors cannot tamper or disable a template or even want to. A good template will provide sufficient styles so that the predominant authoring style (Normal Style or Body Text) does not have to be reformatted to add bullets, numbers or capitalization.

In order to redeem the benefits of template usage, however, everyone including outside vendors must use the official company style and content templates. Enforcement is a major issue. In spite of the wonderful benefits provided by templates, authors are surprisingly resistant to using them and companies spend substantial sums of money and go to great lengths to create restrictive templates and educate authors in their usage. Unfortunately, savvy authors can always find workarounds to sidestep even the most tamper-resistant template. Consequently, more and more companies are augmenting template usage with test publishing and Edit Check programs that validate the final document against template specifications such as

margins, header and footer content and styles.

And that brings us to the next stage in the evolutionary process of the document: the XML file type. Initially, XML may seem more complicated than Word but it meets all the criteria of a “good” template, described above, and presents few of the problems as well. Companies that have invested heavily in templates and macros and were not able to achieve the results they needed, may achieve better results with XML-based authoring.

Whereas a Word document consists of content (document) and form (template), an XML document breaks it down even further into content (document) form (style sheet) and context/structure (DTD). This additional segregation truly separates the mechanics of writing from the format and structure and takes the burden away from the author.

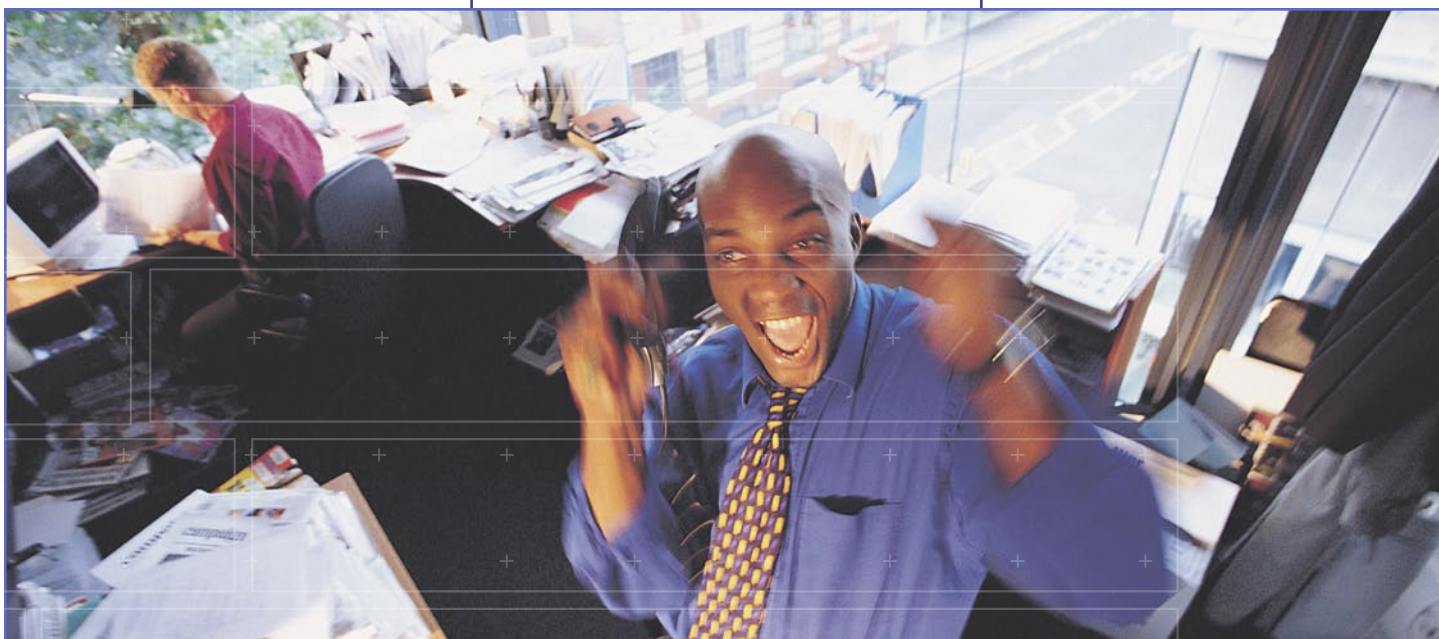
Unlike a template that operates in the background of a Word document as it is being authored, the style sheet is completely separate and is laid over the content when the document is viewed. This doesn't render the style sheet tamper-proof but removes the desire

to do so as it doesn't interfere with the authoring process.

DTDs are powerful tools for organizational standardization in much the same way as templates and style guides. A flexible DTD is like a style guide. Essentially the DTD enforces structure. It provides immediate feedback to the author if the document is out of context or incomplete. Also, the administrator of the DTD has the ability to require information to make documents complete and consistent. This is definitely true for the pharmaceutical industry where the DTDs are actually provided by the regulating authorities.

XML authoring has been viewed with trepidation but, as you can see, there are many benefits. With the advent of Structured Product Labeling (SPL) and the eventual eProtocol requirements, XML will continue to become more commonplace in our industry.

But if you think that's the end of the document (r)evolution, think again. Have you heard about active documents? Well, that's another story.



STANDARDS INITIATIVES ACROSS INDUSTRY

Over the past decade, technology has been rapidly changing the way the pharmaceutical industry develops new therapies. Computer systems and software applications have replaced many manual processes that have long existed to support drug development and the registration of new drug products. In parallel, internal and external pressures on both sponsors as well as regulatory agencies to increase efficiencies and reduce cycle times have continued to mount.

As a result, organizations have been creating drug development standards for industry to follow that will improve overall efficiency by leveraging extensible markup language (XML)-based technology. The increasingly widespread adoption of XML is fueled by its ability to enhance acquisition, exchange, organization, assembly, review, query, and re-use of information.

The following sections provide a high-level description of the organizations developing standards including the geography of their membership, their organizational goals (or focus) and the standards that they are developing.

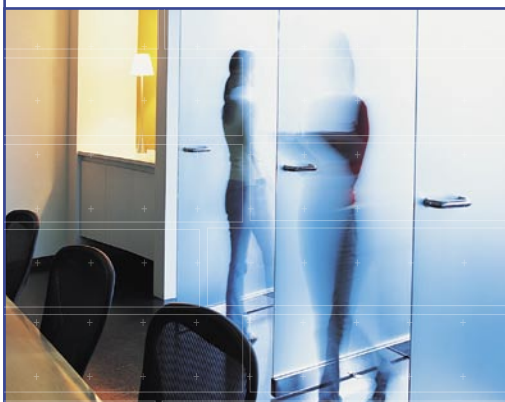
THE STANDARDS ORGANIZATIONS

International Conference on Harmonisation (ICH) ICH is a consortium of regulatory bodies from the United States, the European Union, and Japan, as well as the Observer countries of Canada and Switzerland (as representative for the European Free Trade Area). The organization's primary objective is to harmonize the various regional requirements for pharmaceutical drug product registrations among the member regions.

ICH standards include the Common Technical Document (CTD), Electronic CTD (eCTD), and Medical Dictionary for Regulatory Activities (MedDRA).

Clinical Data Interchange Standards Consortium (CDISC) CDISC is an open, multidisciplinary, non-profit organization committed to the development of worldwide standards to support the use of clinical trials data and metadata for medical and biopharmaceutical product development.

CDISC has developed standards for submission of data, structuring data tabulations, analysis datasets



and laboratory data. CDISC is also developing standards for clinical trial protocols and the exchange of non-clinical data.

CDISC standards include Submission Data Standards (SDS), Structured Data Tabulation Model (SDTM), Analysis Data Set Modeling (ADaM), Laboratory Data Standard (LAB), and Standards for the Exchange of Non-clinical Data (SEND).

Pharmaceutical Research and Manufacturers of America (PhRMA) / SAFE-Biopharma Association PhRMA represents the country's leading pharmaceutical research and biotechnology companies and focus on conducting effective advocacy for public policies that encourage discovery of important new medicines for patients by pharmaceutical

and biotechnology research companies.

PhRMA initially sponsored the Secure Access for Everyone (SAFE) initiative however, in order to include global participation from companies, associations, and regulatory agencies in Asia, the Americas and Europe, the SAFE-Biopharma Association was formed.

Health Level 7 (HL7)

Formed in 1987, HL7 is a not-for-profit ANSI standards development organization (SDO) open to international membership. HL7 develops international standards to support clinical patient care and the management, delivery and evaluation of healthcare services. The standards define data format and content that allows different health information systems to easily and effectively communicate with one another. These standards apply to both research and healthcare activities.

HL7's Regulated Clinical Research Management (RCRIM) committee mission is to create and promote its standards by developing standards to improve or enhance information management during research and regulatory evaluation of the safety and efficacy of therapeutic products or procedures worldwide. The committee defines messages, document structures, and terminology to support the systems and processes used in the collection, storage, distribution, integration and analysis of such information. Some specific areas the committee is developing standards for include clinical trial registries, annotated ECG waveform data, stability data, laboratory results for clinical trials, protocols, regulated product submissions and Structured Product Labeling (SPL).

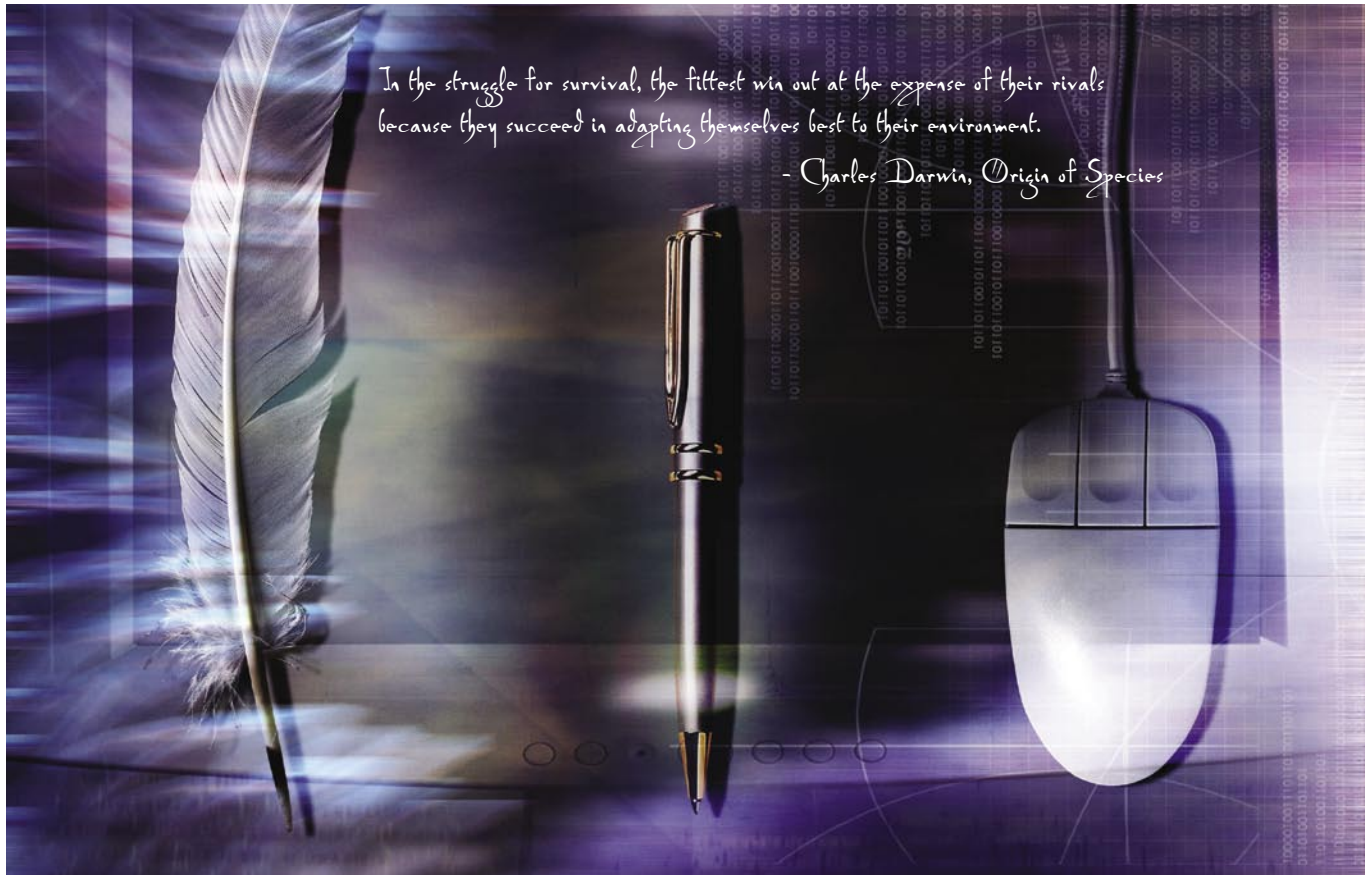
CONCLUSION

External business drivers and the expanding use of technology in drug development have resulted in numerous standardization initiatives. The standards are many, the topics covered are broad

and the future implications are not always clear. However, it is certain that many standards will continue to be developed, recommended and then ultimately mandated by regulatory agencies.

Therefore, it is critical for sponsors to build and maintain awareness of standards that will impact their day-to-day drug development processes.

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:

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- CDISC Registered Solutions Provider
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