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In the next issue of  
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*EDC Management is the leader in Clinical and Data Management and Electronic Data Capture (EDC) consulting services for the biopharmaceutical industry. EDC Management publishes well-researched and timely information about Electronic Data Capture technologies and processes through EDC Today<sup>TM</sup> and EDC In Depth. We do not sell or endorse any specific EDC software application or vendor. Improve process today; position for tomorrow.*

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## EDC and Its Impact on Electronic Submissions

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

*To assist organizations making the transition from paper-based clinical trials to EDC-facilitated trials, our thirteenth issue takes a closer look at the impact of implementing an EDC system on New Drug Application (NDA) or Biologic License Application (BLA) submissions, particularly electronic submissions.*

Submissions to the Food and Drug Administration (FDA) are a critical component of a biopharma's business. With the current changes in data capture and reporting, biopharmas may be adopting electronic submission practices and EDC simultaneously. Many biopharmas have already performed one or more electronic NDA or BLA submission, and have successfully assembled the required electronic representation of paper case report forms (CRFs). Now they need to take subsequent steps for making the electronic CRFs (e-CRFs) used in EDC available for submission.

According to Charles Boersig, in "Why NDAs Fail: 15 Pitfalls and How to Avoid Them", one of the major reasons an NDA might fail is "not thinking about electronic submissions" and he goes on to say:

"New technologies for electronic data capture and global initiatives to develop standardized documentation for new drug applications represent a new opportunity for drug developers to speed reviews and maximize product potential...But making the transition from paper-based reporting to a Web-enabled, real time process requires a significant evolution in clinical research practice...The FDA is working with the industry to phase in electronic submissions as companies gain the required capabilities."<sup>1</sup>

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This issue first reviews the current requirements for an electronic submission when using paper CRFs and discusses the steps necessary for electronically submitting e-CRFs. The issue then discusses a view of the most likely future of electronic submissions and what this means to biopharmas using EDC. Finally, it introduces the FDA’s current Submissions Data Standards (SDS) initiative.

### **Electronic Submissions with Paper CRFs**

When performing electronic submissions for paper-based studies, biopharmas follow FDA guidelines and scan their paper CRFs into Adobe Portable Document Format (PDF) files, and then create bookmarks and hypertext links. The *“Guidance for Industry Providing Regulatory Submissions in Electronic Format — General Considerations”* states:

“Regulations in 21 CFR Part 11 require that the Agency be able to generate from any document provided in electronic format an accurate and complete paper copy that is both legible (“human readable”) and suitable for inspection, review, and copying. Therefore, documents submitted in electronic format should:

- Enable the user to easily view a clear and legible copy of the information.
- Enable the user to print each document page by page, as it would have been provided in paper, maintaining fonts, special orientations, table formats, and page numbers.
- Include a well-structured table of contents and allow the user to navigate easily through the submission.
- Allow the user to copy text and images electronically into common word processing documents.

To achieve the above goals, you submit all electronic documents in Portable Document Format (PDF).”<sup>2</sup>

In the *“Guidance for Industry Providing Regulatory Submissions to CBER in Electronic Format — Investigational New Drug Applications (INDs)”*, the FDA states:

“Case Report Forms (CRFs) are item 12 on page 2 in FDA form 356h.

If a paper CRF was used in the clinical trial, the electronically submitted CRF should be an exact image or series of images of the paper CRF that contains all original entries with all the modifications, addenda, corrections, comments, annotations, and any extemporaneous additions.”<sup>3</sup>

The guidelines in this publication are also pretty clear about how to go about creating bookmarks and hypertext links. The FDA further states,

“Each CRF must have bookmarks as part of the comprehensive table of contents required under 314.50(b). We recommend bookmarks for each CRF domain and study visit to help the reviewer navigate the CRFs.

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For addendum and corrections, making a hypertext link from the amended item to the corrected page or addendum is a useful way to avoid confusion.”<sup>3</sup>

The FDA also lays out additional specific formatting and indexing guidelines for CRFs in a submission. They would like to be able to “cut and paste” text from the PDF files. They have fairly detailed “full text indexing” requirements. In order to index PDF files, using the suggested Adobe Catalog, the document information fields need to be entered/supplied as shown in Picture 1.

**Picture 1. Adobe Acrobat’s Document Information**

General Info

C:\WINDOWS\TEMP\Acr1361.TMP

Title:

Subject:

Author:

Keywords:

Binding: Left Edge

Creator: Acrobat 4.05 Scan Plug-in for Windows

Producer: Acrobat 4.05 Scan Plug-in for Windows

Created: 03/04/2003 11:33:54 AM

Modified: 03/04/2003 11:33:54 AM

Optimized: No File Size (Bytes): 0

PDF Version: 1.3

OK Cancel

A number of PDF-centric tools are available to partially automate the bookmarking, hypertext linking, and indexing processes. Some of these tools rely on searching for particular fonts in particular positions on a page. Other tools allow for batch loading of general information in the document information area of the PDF file. Many biopharmas have worked with Documentum and Core Dossier to help with their electronic submissions, but these document management packages are complex and require significant technical expertise to support and use.

### **Electronic Submissions with Electronic CRFs (EDC)**

One would think that implementing EDC would have a fairly minor impact on electronic submissions, and in fact the guidelines are concise and straightforward. The FDA guidance on NDAs states,

“For data collected electronically, all data collected for an individual patient should be organized by domain and time and provided as a PDF file. This presentation is the same as a patient profile described in item 11 (CRTs) [Case Report Tabulations]. This file should subsequently be handled the same as an imaged CRFs.”<sup>3</sup>

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Thus for e-CRFs, the following is needed:

- The replacement of paper CRFs now scanned into PDF files with PDF files generated by either the EDC implementation from its e-CRFs, or by third party software from the EDC database.
- The ability to provide the FDA with “copies of records” in a way that preserves the electronic signature.
- The ability to provide the FDA with “copies of records” in such a way that:  
    “...the copying process used produces copies that preserve the content and meaning of the record. If you have the ability to search, sort, or trend Part 11 records, copies provided to the Agency should provide the same capability if it is technically feasible. You should allow inspection, review, and copying of records in a human readable form, on your site, using your hardware and software, following your established procedures and techniques for accessing those records.”<sup>4</sup>

Several EDC vendors offer eCRF to PDF support. For example, Phase Forward offers CRF Submit®. According to Phase Forward’s web site,

“The CRF Submit Module enables pharmaceutical, biotechnology and medical device companies involved in clinical trials to automatically generate PDFs of the electronic Case Report Forms (e-CRFs) created in the InForm® system as part of their New Drug Application (NDA). The output of the tool includes the detailed table of contents and bookmarks to comply with FDA guidance.”<sup>5</sup>

Also, Lifetree’s Integrated Clinical Trial Manager® provides “*PDF generation with a single keystroke.*”<sup>6</sup>

As a final example, DataTrak states on its web site, “Single patients, single sites or all sites can be archived in hyperlinked PDF format files.”<sup>7</sup>

## **EDC and the Future of Electronic Submissions**

A more subtle impact of EDC would be the effect on the production (i.e., creation/generation) of electronic submission materials. That is, the process of getting the submission materials collected. An eventual goal would be to have the EDC system directly tied to the document management system in such a way that the e-CRF parts of the submission are automatically generated and included. As Michael Rosenberg, President and CEO of Heath Decisions Inc, states:

“Tying the study system into a framework to facilitate submissions is an important element of minimizing the interval between [study] completion and regulatory submission. Technology now allows seamless integration of electronic clinical trial systems and document management systems.”<sup>8</sup>

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Rosenberg further believes that regulatory submissions can be made a much more simplified task, and could lead to faster time to submissions following database lock. However, he warns “...[a] simple technology such as data collection will not achieve full impact until the multiple complimentary components that lie elsewhere can be aligned.”<sup>8</sup> In other words, Rosenberg believes that all clinical computer systems should be integrated and focused towards a common goal, the production and support of FDA submissions.

Many EDC vendors are providing submissions-related features as part of their products. These features still need to be integrated with any existing or planned document management or submissions management software the biopharma will be using to produce its submission material.

### **EDC and Standards**

Another impact of EDC on Electronic Submissions is related to the changes caused by the use of electronic records and electronic signatures. In particular, EDC has helped to spur new efforts in creating data standards as a way of streamlining data transfers from EDC vendors to sponsor databases. This is especially true of vendors that offer Application Service Provider (ASP) services.

Interest in standards has been long-standing and nearly universal, but for the most part implementations of standards have been limited to data that is internal to an individual biopharma. With the increased need for data transfer, there has been increased support for a general standards body. Clinical Data Interchange Standards Consortium (CDISC) has thrived in recent years, in part, for this reason.

CDISC started by looking at existing standards and available technologies. It then evolved a process of creating standards that involve participants from the biopharma area. Susan Bassion provided a little background about the development of laboratory standards when she stated,

“Existing data standards covering the handling of laboratory data include ASTM, HL7, ACDM, and X12. These standards are not well known in the drug-development community, and with the exception of ACDM, have not been applied to the large volumes of data generated during a clinical trial. Many handle general healthcare and transactional data transfers well, but may be inflexible, inefficient, have inadequate field definitions, or have populations rules that do not align with clinical trials.”<sup>9</sup>

*[Visit the CDISC website, <http://www.cdisc.org/>, for a more detailed description of the history and progress of the organization.]*

Table 1 provides a brief description of some of the terms and acronyms commonly encountered when reading about electronic data transfers.



Table 1. Definitions of Relevant Terms

Term	Description
EDI	Electronic Data Interchange. A technology for transferring data from one computer system to another. EDI has been around for some time and has been used in many different industries.
Protocol	A protocol in computer terms is a formal well-defined standard for exchanging information between computer programs.
OSI	Open System Interconnection. A model for connecting computer systems.
HL7	Health Level Seven is a particular protocol for an EDI that allows information exchange between medical applications. The name Health Level Seven reflects the 7th layer protocol level in the OSI model. HL7 is a protocol for data exchange; it defines the format and the content of the messages that applications have to pass to one another in different circumstances.
XML	Extensible Markup Language is a language that uses tags to identify the content of data.
eCTD	Electronic Common Technical Document. An EDI definition developed by the International Conference on Harmonization (ICH) for data transmissions between the pharmaceutical industry and regulatory agencies. The ICH has developed an XML model for defining submission documents.

CDISC decided to use XML as its representation and file format of standards. As far as EDC and submissions are concerned, there are two CDISC “standardizing” data models of interest. The first is the ODM – the operational data model. This model allows the representation and transfer of clinical data (and its definitions) from an EDC system to another computer system such as a Clinical Data Management System (CDMS). The second model is the SDS – the submissions data model.

**The FDA's Submissions Data Standards (SDS) Initiative**

The FDA has taken a keen interest in the efforts of CDISC. In particular, the FDA is considering the adoption of the SDS for electronic submissions.

In an article for Bio-IT World entitled “Clinical Data Standards Face Uphill Battle,” Brian Reid states :

“The FDA has become more supportive of electronic data submissions in lieu of the truckloads of paper that were once standard practice, and companies have been increasingly willing to follow agency guidance that encourages files in Adobe Acrobat-readable PDF format. But as technology moves forward, experts said that a new paradigm for FDA submissions would be needed to manipulate the data in those filings.

The Clinical Data Interchange Standards Consortium (CDISC) has led that charge. The nonprofit group, which counts 85 member companies, is developing an XML-based standard that would allow raw data to be analyzed without painstakingly copying the information from paper or PDF documents into a data-analysis tool. Though still in its early stages, the group has offered companies a rough framework for how to ease the transition of data from the clinical laboratory all the way to the computer screens of the FDA.”<sup>10</sup>

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In addition to supporting CDISC and the SDS, the FDA is also piloting a Patient Profile Viewer. This viewer will allow the FDA to view patient data in the form of case report tabulations (CRT) datasets. As the FDA states in Docket No. 01N-0496:

“The Food and Drug Administration (FDA), Center for Drug Evaluation and Research (CDER), is seeking volunteers to participate in a pilot project involving the testing of the Patient Profile Viewer (PPV). The PPV is computer software that allows a reviewer to display data collected from case report tabulations (CRTs) submitted in electronic format. We are working with PPD Informatics to develop the PPV under a Cooperative Research and Development Agreement (CRADA) in an effort to improve review efficiency, develop standards for submission of data, and eliminate the need for the submission of patient profiles by applicants of new drug applications (NDAs). To help in this development, we are seeking volunteers to provide CRT datasets from clinical studies to test the PPV. Data supplied during the pilot project will not replace any regulatory requirements for submitting CRTs.”<sup>11</sup>

## **Conclusions**

As EDC use becomes more prevalent, and as the FDA further evolves its thinking about electronic submissions, there will be more changes in the not-to-distant future regarding EDC and electronic submissions. While predicting the future is risky at best, future electronic submissions will likely involve CDISC data tagging and extensive use of XML.

EDC vendors will likely continue to evolve their product offerings to match FDA submissions requirements. Many vendors already have PDF tools in place, and several have XML tools in place to support the CDISC ODM. As the CDISC SDS definition becomes a reality, more vendors will likely support direct creation of SDS XML-tagged data files.

*(continued on page 8)*



References:

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- <sup>3</sup> FDA, *Guidance for Industry Providing Regulatory Submissions to CBER in Electronic Format — Investigational New Drug Applications (INDs)*, <http://www.fda.gov/cder/guidance/2353fnl.pdf>.
- <sup>4</sup> FDA, *Guidance for Industry Part 11, Electronic Records; Electronic Signatures — Scope and Application*, <http://www.fda.gov/cder/guidance/5505dft.PDF>.
- <sup>5</sup> Phase Forward, "Phase Forward Releases the CRF Submit Module for Electronic CRF Submissions for New Drug Applications", <http://www.phaseforward.com/news/pr/2002/020514.htm>.
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- <sup>7</sup> Datatrak, "DataTrak Review™", [http://www.datatraknet.com/master.cfm?site\\_id=772](http://www.datatraknet.com/master.cfm?site_id=772).
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Who's behind the research?

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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