BY DENISE MYSHKO

E-Submissions
On the Brink of Going Paperless

THE SHIFT FROM STATIC PAPER REGULATORY APPLICATIONS TO DYNAMIC AND INTERACTIVE ELECTRONIC SUBMISSIONS will make data more accessible to reviewers and, ultimately, improve the efficiency of the review process.

December 15, 2004, was a day unlike any other at Wyeth Pharmaceuticals. That Wednesday, the company simultaneously submitted a registration dossier in five regions. But what was so unusual was that the submissions were done electronically.

Wyeth officials submitted an electronic common technical dossier (eCTD) for Tygacil to regulatory officials in the United States, Canada, and the European Union, which includes 25 countries governed by the European Medicines Agency (EMEA). Electronic applications also were submitted to authorities in Switzerland and Australia. (For more information, see box on page 45.)

Tygacil (tigecycline) is being developed as an injectable antibiotic for treating serious polymicrobic infections in hospitalized patients when resistant pathogens are known or suspected.

"This is new not only for Wyeth but also for those regions," says Gina Schmidt, director of global regulatory submissions management at Wyeth, referring to the simultaneous electronic submissions. "To our knowledge, this is something that hasn't been done before."

Regulatory agencies across the globe are trying to make the transition from paper to completely electronic submissions. Already the FDA has publicly stated its intent to move in that direction, and other regulatory agencies are willing to work with companies in this regard.

"Our goal is to have all portions of the submission come in electronically," says Randy Levin, M.D., director for health and regulatory data standards at the FDA. "When the submission is done electronically, it is easier to make the information available to reviewers, which makes the process much more efficient."

Wyeth's application to the FDA for Tygacil was entirely electronic. Rather than a paper application, the company delivered a digital linear tape that can be archived and all subsequent communications, including amendments and supplements, also will be submitted electronically.

"With the exception of original signatures, we did not print a single piece of paper for the U.S. submission, and from this point forward we do not intend to print any more paper," Ms. Schmidt says. "This is life-cycle management of a dossier at regulators' fingertips. This format is useful not only for the agencies that are reviewing the dossier but the information is readily available for everyone internally who needs to see it."

According to FDA officials, because an electronic format is more efficient than paper for some submissions, the agency is starting to require electronic submissions in some cases.

"There are certain types of submissions that the agency now requires to be in an electronic format, and we are considering others for electronic submissions," Dr. Levin says. "For example, in June 2004 we changed our regulations to require the content of the labeling to be in an electronic format."

He says the agency is considering implementing a mandate for study data and post-

John Cline

CDISC is leveling the playing field and driving adoption standards across all fronts of the drug-development process.

marketing adverse events to be submitted in electronic format.

"Postmarketing adverse-event reports are probably the most frequent single type of submission the agency gets," Dr. Levin says. "The FDA receives hundreds of thousands of these types of reports a year. So, we are looking at requiring those reports to be electronic."

Similarly, Europe is pushing toward requiring electronic submissions in some cases. In March 2004, in the official journal of the European Union, it was specified that reporting of suspected unexpected adverse reactions should be transmitted electronically in the form of a report, other than in exceptional circumstances.

Agency reviewers want to be able to look at the data every way they can; they don't want to have to go back to the sponsor every time they have a question, says Mark H. Bradshaw, Ph.D., VP of global biometrics and data management at Covance Inc.

"If the answers were not provided in the normal paper submission, the reviewers would have to go to their statistical group to get the information, which could take a long time to get a response," he says. "Or they would send the questions to the sponsor, but then they were concerned about being able to replicate the results."

The Benefits of E-Submissions

The FDA accepted the first electronic new drug application in 1991: a 55,000-page summary document that included data from more than 20 million pages of material created over 13 years, stored on 175 CDs and submitted on a Sun Solaris operating system using Oracle, Documentum, and SAS application software.

Since then, pharmaceutical companies have made significant strides in updating their systems and shifting to an electronic environment. Dr. Levin says for most new drug applications, at least part of the submission is electronic.

"We would like sponsors to recognize the advantages of electronic submissions and move toward using electronic files for their processes," he says. "For the agency, it is so much easier to process applications electronically than to receive a truckload of paper."

Electronic submissions not only make for a much more efficient review, but they may also be less expensive. According to a recent KPMG report, in the United States the cost per page of data submitted electronically to the FDA is $4.50 as opposed to $23 per page for paper-based submissions. In that same report, Novartis claimed that moving clinical-trials data to computer networks reduced the cost of data management by as much as 82%.

Update on Standards

Industry leaders say the move toward industrywide standards is making the shift to electronic submissions a reality. The development of standards, such as the Clinical Data Interchange Standards Consortium (CDISC), Health Level 7, and the International Conference of Harmonization (ICH), is leading the way toward standardization throughout the healthcare industry.

The pharmaceutical industry is in the midst of a transition, with companies retooling processes even though many types of data have yet to be defined under these models, says Michael A. Walega, executive director, global biometrics operations, late-stage development services, at Covance.

"Companies are going to go forward with their electronic marketing applications before the standards appear because their shareholders are demanding improved efficiencies," he says.

In the United States, regulatory authorities have been the driving force for this transition. In 1999, the FDA issued a guidance about formatting electronic submissions in an effort to create standards. Additionally, former FDA Commissioner Mark McClellan, M.D., Ph.D., had publicly stated his support for the CDISC standards while he was in that post.

"The 1999 guidance was based on the use of tables of contents in PDF format," Dr. Levin says. "The other way to submit applications is based on the electronic common technical document specifications. The eCTD contains specifications for arranging files, although it is not specific to the file itself, and how to create a series of XML files that contain metadata about every file that is submitted. We use

James Walker

Companies need to embrace the fact that electronic submissions go beyond being just a regulatory concern. This process is a fundamental shift in the way the entire company does business.

Michael Walega

Standards have evolved to promote more effective use of the information collected during the conduct of clinical trials to enhance the ability to rapidly analyze and interpret that information to assess the safety and efficacy of disease therapy candidates.

Dr. Randy Levin

If sponsors start to build e-submissions into their strategic plans, everyone will be better off. They will start to gain the advantages of electronic files, and reviewers will have better access to data.

Dr. Mark Bradshaw

The classic tenets of project management apply: careful resource management, time management, and risk management.

those metadata to create a table of contents for the submission and to manage the different submissions related to an application that come in over time."

A separate specification associated with the guidance for electronic submissions of applications for human pharmaceutical products and related submissions addresses specific file types, for example submitting study data based on the CDISC Study Data Tabulation Model standard, Dr. Levin says.

"The agency would like to move toward standards and standardized ways of submitting information for a number of reasons," he says. "Right now, we are transitioning from submissions data based on the 1999 guidance, which outlined how documents should come in as PDF files, how data sets should be in SAS transport files, and how things should be arranged in folders."

In April 2003, CDISC released version 3.0 Submission Data Domain Models. These models were developed by the CDISC Submissions Data Standards (SDS) Team, which includes more than 20 active members representing major pharmaceutical companies, contract research organizations (CROs), and FDA liaisons to CDISC.

In June 2004, the organization released version 3.1. This consists of two documents: the Study Data Tabulation Model (SDTM), which represents the underlying conceptual model behind the SDS standards, and the CDISC V3.1 SDTM Implementation Guide (SDTM-IG), which includes the detailed domain descriptions, assumptions, and examples.

In July 2004, FDA officials announced that they would accept applications based on these CDISC standards. The adoption of the standard is consistent with the FDA's Critical Path initiative, which is expected to help automate the largely paper-based clinical-trials research process and foster easier communication and collaboration among clinical researchers. By providing a consistent framework and format for clinical-trial information, this standard is expected to enhance data integration opportunities and thereby help to reduce data management barriers for sharing the latest clinical-trial data.

Additionally, last year CDISC renewed its relationship with HL7, and this relationship is leading to a convergence of standards throughout the healthcare industry. HL7 is focused on standards and interoperability for healthcare systems, while the focus of CDISC is on clinical research. Their activities, however, are becoming increasingly complementary.

The shift toward CDISC standards and eCTD means that sponsors are going to have to

change the way they interact with the FDA and how they do things internally, says Kirk Gallion, chief operating officer at Octagon Research Solutions Inc.

"This is probably one of the biggest shifts in the way that the industry has been doing business," he says. "I wouldn't say this is an overnight revolution, but it is an evolution in processes that are going to radically change the way the industry does business."

According to James Walker, CEO of Octagon Research Solutions, e-submissions will fundamentally shift the way an entire company does business, but companies will realize efficiencies from electronic submissions.

Companies will have to change their systems to maintain interconnected information processes that span years if not decades.

"Data will have to be linked together accurately, cross referenced, and supported," Mr. Gallion says. "Every transaction and every message sent to the FDA will have to be validated against information previously sent. The benefit is that companies won't have to resend information. The down side is that all the information from a metadata perspective has to be completely accurate. Because electronic submissions have hundreds of thousands of points of navigation, this can't be accomplished in the last couple of days or the last few weeks before a submission. The eCTD is forcing new management tools to be deployed to maintain that continuity across years — not months."

CDISC is a great initiative, says John K. Cline, CEO of etrials Worldwide Inc.

"Standards drive adoption across all fronts of a regulated process, such as drug development, and they level the playing field," he says. "While CDISC is being embraced by some sponsors and feared by others, it is a force that is beginning to be recognized for common data interchange. To accelerate the process, we as providers have to learn how to link all the information from the collection stage, through database lock, and to the submission phase."

Challenges of E-Submissions

There will need to be a fundamental shift within the industry. With the emergence of e-submissions, the process is no longer just a regulatory affairs or regulatory operations concern.

Wyeth's e-submission for Tygacil

WYETH PHARMACEUTICALS BEGAN DEVELOPING ITS ELECTRONIC SUBMISSION STRATEGY FOR TYGACIL ALMOST FROM THE BEGINNING. TYGACIL IS BEING DEVELOPED AS AN INJECTABLE ANTIBIOTIC FOR TREATING SERIOUS POLYMICROBIC INFECTIONS IN HOSPITALIZED PATIENTS WHEN RESISTANT PATHOGENS ARE KNOWN OR SUSPECTED. THE CHEMICAL WAS FIRST SYNTHESIZED IN 1992, AND IN 1998 THE COMPANY SUBMITTED AN IND.

1992
The chemical was synthesized.

1998
The company submitted an IND.

Throughout 2004
Wyeth's regulatory department worked with the various internal groups to coordinate the data, which includes the statistical analyses, study reports and supplemental tables, and summary documents. At the same time the label was being developed.

In September 2004
Wyeth officials submitted the quality module to U.S. regulatory officials. This included information about how the company makes the product. At this time, Wyeth paid the user fee for the submission.

In October 2004
The preclinical module was submitted with information about animal testing and toxicology. Also, in October, the company submitted a preview of the clinical data from two studies.

By December 15, 2004
The remaining data were submitted, including all data from four large trials conducted in 43 countries that enrolled more than 5,000 patients. On that day, Wyeth officials also submitted a CTD for Tygacil to regulatory officials in Canada and Europe. Electronic and paper applications also were submitted to authorities in Switzerland and Australia. These regions do not have laws that allow for rolling submissions. In all, applications were submitted in 29 countries.

According to Joan Korth-Bradley, project manager for Tygacil, within Wyeth about 15 different disciplines were involved in the development of the application, including discovery, chemical development, drug safety and metabolism, clinical pharmacology, project management, public affairs, and clinical development in Europe, the United States, and the other countries. The regulatory department coordinated the submission process and developed the submission strategy. Regulatory affairs worked with marketing as well to make sure the commercial goals were met.

Joan Korth-Bradley

Wyeth' e-submission for Tygacil is based on the International Conference on Harmonization's electronic common technical document (eCTD). In the United States, the company is using a rolling regulatory submission process for Tygacil.

Gina Schmidt

E-submissions are the future. They eliminate the need for paper and create better life-cycle management of a dossier.

Kirk Gallion

eCTD is forcing new management tools to be deployed to maintain continuity across a process that spans years — not months.

"Pharmaceutical companies have to overcome a culture based on isolationism," Mr. Gallion says. "Many major companies are organized along departmental functions, which don't consider what is going on parallel to, or outside of, that function. There will have to be more consideration for the entire process. Sponsors can't take a paper-centric process and throw a technology at it and expect the process to be successful. Companies need to fundamentally look at the way they put electronic submissions together and aggressively reach upstream into the functional areas to be able to determine what possible adjustments need to be made."

CDISC standards need to be designed into the e-submission process, Dr. Bradshaw says.

"The best way for sponsors to save time and money is to have the process based on CDISC from the beginning," he says. "The worst situation for a company is to arrive at the end of the submission process and then decide to do a massive conversion project. E-submissions require rethinking the way all these data are structured."

Mr. Walega says often a lot of additional time and money are spent in an effort to meet standards after the fact.

"There is a potential pain point here if companies restructure their data just before submission to meet the CDISC approach," he says. "There must be an assurance that analyses performed on different data structures can then be represented and reproduced using the CDISC SDTM structure. This adds unnecessary time, effort, and additional points of entry for inconsistencies and confusion."

Mr. Gallion says developing an e-submission is not about generating a piece of XML, which is a relatively trivial part of the process. Rather companies will have to have the tools to track what's being submitted, where, and by whom and that are designed to integrate functions within the pharmaceutical enterprise.

"Because of the increasing cost of drug development overall, companies will have to use business process management to help drive these processes and optimize the resources they have," he says. ✦

PharmaVoice welcomes comments about this article. E-mail us at feedback@pharmavoice.com.

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