BY TAREN GROM

IMPROVING

THE REGULATORY SUBMISSIONS PROCESS

THROUGH E-STRATEGIES

The inability to effectively manage complex submission documentation for new drug applications (NDAs) and other regulated dossiers is a major factor in slowing the time it takes to bring a product to market.

These delays cost the life-science industry millions in potential revenue. Electronic submissions can speed the process, but the industry continues to struggle with functional isolation issues, a lack of standards, and shifting regulatory guidelines.

> One of the biggest obstacles in the submission process is the systems and standards that were in place during the initial phases of data collection and documentation will have changed. So in the end, a company is left with legacy systems, legacy databases, or legacy data that don't conform to today's submission process standards.
>
> **LUKAS MAKRIS**

UNTIL RECENTLY, ALL REGULATORY SUBMISSIONS WERE DONE AS HARD COPIES, REQUIRING HUNDREDS OF VOLUMES — 500 TO 1,000 VOLUMES — CONTAINING THOUSANDS OF PRINTED PAGES — 250 TO 300 PAGES PER VOLUME. Using current technology, the entire submission can now be produced and submitted to regulatory authorities electronically.

The amount of time and paperwork involved in a successful late-stage clinical trial, which ultimately results in a submission, is mounting. Ensuring that all facets of the process are done right is a time-intensive job. With more than 50,000 clinical trials currently under way in the United States, there is an increasing need to streamline the process.

The release of the FDA's guidelines for 21 CFR Part 11 in 1997 opened the door for companies to implement technologies that reduce the time it takes to publish and approve submissions.

The FDA established 21 CFR Part 11 to ensure the accuracy and security of manufacturing data. One goal of the rule was to make electronic records as secure as paper versions and protect them from mistakes, fraud, and destruction. Industry experts estimate that manufacturers still have between 80% and 90% paper-based processes in validated operations, presenting an urgent demand for paper conversion capabilities. The FDA is pushing to issue its final 21 CFR Part 11 guidance by June 30, 2003 (see related box on page 16).

An additional component to the submission process is the common technical document (CTD) and the eCTD. The International Conference on Harmonization (ICH) — Multidisciplinary Group 2 (M2) Expert Working Group (EWG) — was established to facilitate international electronic communication by evaluating and recommending, open and nonproprietary — to the extent possible — electronic standards for the transfer of reg-

SHIFTING THE PARADIGM ...

MARYBETH CLARK. Director of U.S. customer services, CDC Solutions Ltd., Conshohocken, Pa.; CDC Solutions is dedicated to delivering technology solutions that enable customers to meet the strict standards of regulatory authorities across the world, helping them achieve quality, accuracy, and data integrity to deliver reports and submissions reliably and on time. For more information, visit cdcsolutions.com.

JASON CLEGG. Director, marketing communications, Document Control Systems Inc., Salt Lake City; Document Control Systems develops software that is designed for managing controlled documentation in FDA regulated and other manufacturing environments, the integrated product suite provides a complete solution for document life-cycle management through document creation, approval, electronic publishing, and distribution, including validation and 21 CFR Part 11 compliance. For more information, visit mastercontrol.com.

LAURA FERRIS. Product manager, E2B Gateway, Aris Global LLC, Stamford, Conn.; Aris Global creates a sustainable competitive advantage for customers through the development and deployment of innovative and Web-based software solutions that accelerate drug development and assure global compliance. For more information, visit arisglobal.com.

SUSAN GALLE. Executive director, regulatory strategies, Liquent Inc., Fort Washington, Pa.; Liquent provides content assembly, publishing, and regulatory intelligence technology solutions for the life-science industry. For more information, visit liquent.com.

SYDNEY GILMAN, PH.D. VP of regulatory affairs and quality assurance, aaiPharma Inc., Wilmington, N.C.; aaiPharma is a science-based specialty pharmaceutical company with more than 22 years of drug development experience. For more information, visit aaipharma.com.

LUKAS MAKRIS, PH.D. CEO, BioCor, Yardley, Pa.; BioCor is a benchmark clinical-research organization that offers clinical-data services and consulting to pharmaceutical, biotechnology, medical-device, and venture capital companies worldwide. For more information, visit biocor.com.

RONALD F. TETZLAFF, PH.D. President, KMI Consulting Services, a division of Parexel International LLC, Waltham, Mass.; KMI employs a team of former FDA investigators and experienced engineers, and integrates its established methodologies and innovative information systems to partner with clients in sustaining compliant and high-quality regulatory environments throughout their product life cycles. For more information, visit kminc.com.

JAMES C. WALKER. President and CEO, Octagon Research Solutions Inc., King of Prussia, Pa.; Octagon Research is a process-centric solutions provider that offers a suite of regulatory electronic submissions, regulatory affairs, clinical-data management, statistical, and information technology services to the life-science industry. For more information, visit octagonresearch.com.

SHANNON WILLIAMS. Director, regulatory affairs, PRA International, McLean, Va.; PRA International is an international drug development organization with 2,000 employees worldwide and strong therapeutic expertise in the following categories: oncology, central nervous system, allergy and respiratory, cardiovascular, and, infectious diseases. For more information, visit praintl.com.


MARYBETH CLARK

ulatory information (ESTRI) that will meet the requirements of the pharmaceutical companies and regulatory authorities.

The M2 EWG has provided valuable functionality to the diverse international information exchange needs identified by the members of the three ICH regions, Europe, Japan, and the United States. The M2 EWG recommendations provide a well-defined approach for the evaluation and recommendation of standards. The M2 tasks have led to the recommendation of various open international standards that allow for the international transmission of information regardless of the technical infrastructure.

The recommendations provide solutions for structured messaging; electronic data interchange (EDI); data definitions to incorporate structured data formats, like SGML; security to ensure confidentiality, data integrity, authentication, and nonrepudiation; documents to handle heterogeneous data formats; and physical media for storage and transferability of data.

As companies continue to grapple with these myriad challenges, industry experts say without well-established processes for electronic or paper-based submissions, there will continue to be roadblocks.

To overcome these obstacles, companies need to cut across the various silos — content providers — that are involved in the process. A company's regulatory affairs and regulatory operational groups, including the clinical group, the preclinical group, the toxicology group, the physician group, the regulatory affairs group, the biostat group, the clinical programming group — any group that is writing document summaries — need to be able to pull together and adhere to submission standards.

BREAKING DOWN SILOS

GALLE. Companies should make sure that all of their content creators are included in the documentation process. In our experience, companies tend to think of regulatory operations — the people who put the documents together — and about clinical operations, because the largest portion of information that is included in an application is clinical documentation. But there are other content creators inside and outside the organization. For example, how companies work with their CROs often is an afterthought, which is a big problem. Companies end up with big chunks of information that either don't have the source documentation in an electronic format or if the source documents are available electronically, they may not have been created according to corporate templates and will require rework. Additionally, companies need to include the people who do the Phase IV work in any of the plans or changes to processes. It's great to have an eye on the prize of getting the submission together and getting it out the door to get a product on the market, but often there's a lot of work that happens after the fact for additional indications or other dosage forms, and so on. Essentially, there is a silo approach between central research and the Phase IV group. It's very important to break down those silos so that everybody is able to leverage the same tools and data to be as efficient as possible.

> A document's format, the way things are referred to, and the margins all need to be consistent thereby **FACILITATING A SMOOTHER AND QUICKER REVIEW**.


LAURA FERRIS

GILMAN. If all disciplines within a company had a working knowledge of what is required as documentation for a NDA and supplied this knowledge to the final format, working time to "build" the NDA would be shortened significantly. To that end, companies need to employ training, training, and more training. There needs to be training of all company disciplines so that all involved in the submission process possess a demonstrated knowledge of what is required in terms of the documentation that makes up a NDA: what documentation is always/typically required; what issues need to be addressed; and the format of documentation. Companies need to change the paradigm or mindset that "I just need to get my portion of the job done, regardless of what is needed."

CLARK. I've been in regulatory operations for more than 10 years, and it's always the same scenario: the pulling together of all the components falls to regulatory affairs and regulatory operations. The people who are actually doing the writing and the authoring of the documents often do not look at the big picture. They are probably writing five documents at the same time. Or there might be four or five different writers working on the same document at the same time. Many times, I've found that the authors don't see the big picture, because they never see the completed submission. I believe that everyone who contributes to a submission should see what the end point looks like — whether it's electronic or paper. Everyone should be striving for the same goal. It's not that the authors or writers don't care about standards or preferences; it's that they are focused on their own piece of the puzzle.

WALKER. The earliest work that's done in the development process — preclinical, clinical, and chemistry and manufacturing — often is forgotten until the end. Data were submitted as an IND on paper and nobody thought about

> It would be great if companies could implement a technology, create the reports, and send them in the same way to every single regulatory authority, **BUT THAT'S NOT THE CASE**.

how this information was going to be used as part of an electronic submission. So what happens is that someone has to go back and scan the data, then manually bookmark them and manually hyperlink them. If those functional areas were brought into the process early on, life would be much easier down the road. But most people don't think like that. They are thinking only about their own functional area. Clinical says it's not going to do any regulatory work, because it's not in its budget. But what is not understood is the bigger picture — that the organization could benefit from time and money savings. The whole industry suffers from functional isolation. There's no reason, espe-


John Yee

New Techniques to Simplify the Clinical-Trial Process

THE ASSOCIATION OF CLINICAL RESEARCH PROFESSIONALS' (ACRP) FIRST FUTURE TRENDS COMMITTEE INNOVATION CONTEST was developed to honor forward thinkers in the clinical-research and development industry whose ideas spark a transformation "to do things better, smarter, cheaper, and faster, yet still within regulatory boundaries."

According to the association, the amount of educating, recruiting, reporting, and paperwork involved in a successful clinical trial is mounting. Ensuring that it is all done right is a time-intensive job. With more than 50,000 clinical trials currently under way in the United States, there is increasing need for innovations in streamlining the clinical-trial process. A white paper released by the ACRP's Future Trends Committee recognized the most innovative ideas submitted for its "Tipping Point" contest, which was inspired by Malcolm Gladwell's popular book "The Tipping Point: How Little Things Can Make a Big Difference."

The winners were recognized during a presentation at the ACRP's 27th annual North American Conference and Exposition in Philadelphia on April 8. The association's goal is to bring attention to these innovative ideas and enable them to reach their own "tipping points" and gain widespread use and adoption across the industry. Such innovative ideas will empower clinical researchers to work more efficiently and continue serving as the gateway for tomorrow's needed therapies.

The following are the winners of the association's "Tipping Point" contest:

FIRST PRIZE WINNER — Good Recruitment Practice, submitted by John Yee, M.D., MPH, of BBK Healthcare Inc. Dr. Yee's new initiative sets forth a set of principles and standards for improving 1) the recruitment of patients as study participants and 2) the productivity of healthcare workers as research professionals through the application of best practices in clinical research, marketing science, and health communication.

SECOND PRIZE WINNER — Research Management Software, submitted by Andrew T. Snyder of St. Paul Heart Clinic. Mr. Snyder's new operational software application is designed to enable various users to manage the finances at all stages of a clinical-research program. The software can schedule visits for 1,000 participants, track their progress in each clinical trial, control cash flow, identify work completed and generate current asset reports, invoice payers and sponsors, and forecast future revenue and cash-flow metrics.

THIRD PRIZE WINNER (TIED) — TrialPoint Software, submitted by Samuel W. Hume of Quadragen Inc. Mr. Hume's new software allows clinical research associates (CRA) to track essential documents at clinical-trial sites more efficiently. This application is for use on personal digital assistants, such as Palm Pilots, and replaces the paper and ad-hoc spreadsheets currently used by the majority of monitors. TrialPoint can be integrated into an organization's information infrastructure, making information easy to transfer. It can scan data for invalid and illogical information and compliance issues and it is fully validated for use in a regulated environment. In addition, CRAs can simply use TrialPoint for tracking study checklists, making trial management more efficient.

THIRD PRIZE WINNER (TIED) — Intranet-Based AE Reporting System, submitted by Madeline O'Connor, Ph.D., R.N., at St. Jude Children's Research Hospital. Dr. O'Conner's idea is for a system that enables rapid identification and timely reporting of adverse events to the institu-

FIRST PRIZE WINNER

The Good Recruitment Practice initiative aims to foster awareness of, and provide education about, clinical research while improving communication between the parties involved. It aims to increase patients' and physicians' participation in clinical research and enables patients to make better-informed decisions about clinical-research involvement. Furthermore, **GOOD RECRUITMENT PRACTICE SHOULD HELP REDUCE DELAYS AND COSTS IN DEVELOPING DRUGS, DEVICES, AND OTHER TREATMENTS**.

cially in an electronic world, to have disjointed processes. There has to be a seamless flow. Electronic submissions have to be looked at from a holistic approach. The problem is that there are a lot of vendors and companies that are just thinking about providing solutions for specific functional areas and that's just not a successful strategy. People view the electronic submissions as an IT issue, but it's still a regulatory submission. Companies need to exploit the great tools that are available, but the tools don't supercede the process. And the process is even more important now, because another element is being added — the electronic element.

GALLE. It's difficult to get all factions working toward the same goal. For example, if a person's job is method validations in the chemistry area, there isn't time in his or her schedule to put together a report, let alone a report that complies with specific standards. Putting the documentation together is often an afterthought, and it might not be clear to that person how a new way of doing things is going to make his or her job easier. Companies often don't allow enough time for training, which is one of the primary reasons there is resistance. Companies need to do a better job of explaining why certain processes and standards are necessary in an electronic world — the answer can't be "because regulatory says so." Companies need to explain why an electronic IND is important and what it means to the company in terms of efficiency in getting documentation together and getting it out the door. Once people have a better understanding of the overall goal, there is a better chance for success.

TETZLAFF. Applications often are prepared by staff in the regulatory affairs (RA) department who are responsible for deciding what data to submit and in what format to meet FDA expectations. By necessity, the RA staff relies on information and reports provided by various organizational units within the company. Unless responsibilities for data integrity have been clearly established and understood by all, there is a high probability that checks for integrity may be incomplete or lacking because people did not understand that they had "ownership" for information and data contained in the Chemistry Manufacturing and Controls (CMC) section of a NDA. Unless companies have established data integrity as a core company value and have clearly defined responsibilities for data integrity for each quality system, there is the probability that incomplete or inaccurate results will be submitted in the CMC section of a NDA.

RONALD TETZLAFF

For FDA reviewers, nothing is fundamentally more important than the ability to **MAKE DECISIONS BASED ON DATA THAT ARE ACCURATE, TRUTHFUL, AND COMPLETE**.

WALKER. The functional areas are being asked to deliver completely new deliverables and it's not just about format. It's not about taking the clinical study reports and sending them to the regulatory authority as a PDF file. Companies are having to change the way they write the clinical study report to extract all the efficiencies out of the electronic processes. The functional areas need to be better educated about what "submission ready" means and what they need to deliver to regulators. A company isn't saving time if regulatory is kicking documents back to the functional areas constantly. On the regulatory side, the same could be said. There are guidances, but of course with any guidance there are ambiguities and interpretations.

MANAGING THE PROCESS

TETZLAFF. For FDA reviewers, nothing is fundamentally more important than the ability to make decisions based on data that are accurate, truthful, and complete. Companies that establish quality-system programs to focus on data

tional review board (IRB) that meet criteria for expeditious review. Furthermore, the adverse event can be reviewed by all principal investigators working on all protocols associated with the study participant. This system is designed to accommodate the complex relationship between multiple protocols, multiple departments, and the individual study participant. It also facilitates expedited reporting to the various federal agencies overseeing clinical-research projects while eliminating unnecessary paperwork and redundant reporting.

THIRD PRIZE WINNER (TIED) — Competency-Based Orientation (CBO) Tool, submitted by Claire M. Berg, of the Maine Medical Center. Ms. Berg's tool is designed to meet the goal of providing new clinical research coordinators (CRC) with the necessary knowledge, skills, and attitudes to function effectively in their role. This self-directed learning program is based on the ACRP CRC Task Survey and ensures that CRCs are knowledgeable in all situations. The CBO tool is a multipage document given to coordinators while in orientation. It includes all the written materials, audio, and videotapes that can help CRCs learn the skills they need. The tool can be transmitted electronically and can easily be modified to meet the needs of any research site.

Dr. James W. Maloy, ACRP member and white paper author, says he hopes these ideas will serve as inspiration for more innovations in the clinical-research process.

Source ACRP, Alexandria, Va.

integrity as a core company value are more likely to have successful outcomes for complex regulatory filings. As the complexity of data and documentation increases so does the likelihood of errors and omissions that may lead to compromised integrity. The most effective way to manage complex regulatory filings is to develop and implement effective quality systems to ensure that responsibilities for data integrity have been clearly established at all management levels. As a core company value, data integrity must be designed into every quality system as a fundamental element from the point when results are originally captured. For example, raw data from observations, measurements, or analytical tests until such results are submitted in the CMC section of a NDA.

CLEGG. A submission can consist of more than 600,000 pages. Often new information is added, which changes the pagination. So imagine what this would mean for a paper-based system, especially when updating for last-minute changes. This can take a considerable amount of time using a manual process. In an electronic system, ad hoc changes to the submission can be done quite easily and the submission is automatically updated. If two or three days can be cut from the product commercialization process it could potentially save the sponsor millions of dollars.

WALKER. Companies need to stop thinking about submissions strictly as a regulatory issue or strictly as a clinical issue. There needs to be a process and the process needs to start at the beginning of a clinical-trial program. It's about taking electronic submission methodologies and pushing them across the organization, not just one segment of the organization. Anytime people hear submission they think it's a regulatory concern, which in a paper world maybe it was. But in an electronic world, it's an organizational concern. This is an example of something that could cause a lot of rework and problems. Within a clinical study report, if just a simple cross-referencing strategy is not done consistently across the whole study report, those references have to be hyperlinked manually rather than electronically. Technology can't do the thinking. For example, technology can be designed to search

21 CFR Part 11: An Update

"We don't want to leave industry hanging without specifics" on how to interpret Part 11,says Joe Famulare, director of the FDA's Division of Manufacturing and Product Quality. He says the agency could issue the guidance as early as a month after the comment period expires on April 30.

The FDA in February issued a draft guidance that withdrew all prior Part 11 draft guidances and indicated that the agency would narrow its scope when enforcing the rule. Mr. Famulare says the agency intends to "go forward on the path we put forth in the [February] guidance," but adds that agency officials could issue additional guidances on specific topics if industry comments demonstrate a clear need for that.

In early comments, companies have asked the agency to clarify what it means by "narrow scope." For example, Ernst & Young said in its March 26 comment letter: "The agency intends to exercise enforcement discretion for Part 11 requirements on validation, audit trails, legacy systems, copies of records, and record retention … but there is no indication of how this will be performed. It is not clear whether the intention is that the discretion is to be executed by investigators, based on their best knowledge, on a system-by-system basis, or if the intention is that execution will be based on criteria defined in agency guidelines."

Mr. Famulare says the agency is asking industry and groups such as the 21 CFR Part 11 Coalition for their input.

THE FDA IS PUSHING to issue its final **21 CFR PART 11 GUIDANCE BY JUNE 30, 2003**, according to an FDA agency official who spoke to the *Part 11 Compliance Report*.

"One of the reasons we went right to the guidance [in February] was we wanted to signal a path forward pretty quickly," Mr. Famulare says.

A big part of that path is a "more flexible approach" that will allow regulated life-science firms to assess the degree of risk associated with each electronic record and establish appropriate controls based on that risk, Mr. Famulare notes.

But equally important, he says, is for industry to understand that the agency's new risk-based and narrower interpretation of Part 11 does not mean the industry won't enforce the rule or has lost interest in it.

"The importance of e-records integrity is still there," Mr. Famulare says.

He adds that the agency made a point of stressing the importance of predicate rules in the Feb. 20 guidance.

Others have zeroed in on specific issues. In its comments, Apotex Research executives have asked the agency to address periodic verification of a software system for Part 11 compliance, a practice that the draft guidance does not address.

QAD executives have told the agency that its "premise that Part 11 has had unintended consequences is certainly well founded," and has called the original rule "problematic at best."

But QAD executives say the new guidance does not "cover the waterfront with respect to the entire scope of Part 11." It has called for further agency clarification in a number of areas, including electronic signatures.

Source:FDA, Part 11 Compliance Report, April 16, 2003

for a string and to then hyperlink that string to the study report automatically, but if that string is not consistent, it can result in additional time. This is a trivial example, but it speaks to the broader issue that people at all levels of the organization need to think about electronic submissions when they are doing their jobs, because that's when time is saved.

GILMAN. Potentially untrained regulatory personnel should not try to interpret and explain a situation from a discipline wherein they may not have any regulatory expertise. Personnel from the discipline from which the issue is best understood should address the issue completely and supply that resolution to the regulatory authority for inclusion in the application. Quality pre-planning in the genesis of a project would save significant time and finally routine, good communication among all team members would prevent a great deal of wasted time.

TETZLAFF. In my opinion, the biggest obstacle in submitting an application to the FDA is the failure to adequately define who — for example, which production and control departments — is responsible for maintaining documented evidence that the application contains information and data that are accurate, truthful, and complete. Managers who are responsible for the content of an application must rely on data that are generated and captured in a multitude of quality systems over a period of many years — sometimes up to 10 years.

SUSAN GALLE

Any content that is created today without CTD in mind is instant legacy. **THERE'S NO REASON NOT TO CREATE CONTENT ACCORDING TO ICH GUIDELINES.**

GILMAN. Knowing and understanding precisely what the FDA expects is a big obstacle in the submission process. Receiving full, complete data packages from the different disciplines within a company is another. Training people to think outside of the "tunnel" from which they work and to obtain the information/data that are required is yet another obstacle. The final compilation typically comes down to a crunch time wherein there is a rush to write and compile the submission under last-minute conditions. Typically, most other areas of the project slip, but the ultimate timeline does not. There is significant difficulty in obtaining consensus on strategy and content of a submission by team members and client.

MAKRIS. Many times when there is a migration from one system to another, in this case from paper to electronic, there is a tendency to replicate the system. In essence, groups try to replicate the deliverables from a paper-based system with an electronic system, and that's not necessarily the right approach. When the process is changed, it's better to rethink all the outcomes instead of trying to replicate an existing process.

WILLIAMS. Pharmaceutical product development currently is experiencing a paradigm shift from a paper-based foundation to an electronic one. This is most apparent in areas such as electronic data capture (EDC) and electronic publishing of investigational and marketing applications. And anytime there is a shift in the paradigm by which major processes such as drug development operate, there is a lot of uncertainty. I think the general feeling of uncertainty that currently seems to prevail in pharmaceutical product development is a reflection of this shift from a paper-based to an electronic paradigm. Adding to the complexity of this transition, especially in the area of electronic publishing, is the concurrent emergence of the CTD format as the global standard for marketing applications. The ICH processes and the shift to an electronic environment have converged to create the perfect storm. In addition, the myriad emerging regulations and efforts to standardize the language of pharmaceutical product development, i.e., the ICH process, European mandates for use of the CTD as the standard format for submission of applications, and initiatives such as the Clinical Data Interchange Standards Consortium (CDISC) only have served to increase its intensity.

WALKER. Because of all the electronic transactions that are going on with multiple regulatory authorities, we are talking about managing hundreds of thousands of pieces of content as well as hundreds of thousands of bookmarks and hyperlinks and navigational tools. There are a lot of technology vendors providing tools to help companies execute those tasks. But what isn't provided, and one of the reasons why in some cases it takes longer to do some submissions, is that nobody is coming up with a way to track deliverables; to track issues, resolutions, and approvables; and to develop processes in concert around those tools. Companies are looking at electronic submissions too much as an IT issue rather than as a process and functional issue. That's been a big challenge for every organization that is trying to implement the new policies and procedures.

CREATING STANDARDS

MAKRIS. Establishing standards three months before submission is too late. Companies can easily start to implement standards at the beginning of a Phase III program — by bringing back all the reports from the previous studies and taking a good look at all of the differences between the documents. It is more achievable for companies to establish standards at this point than at the beginning of a program. It is very difficult for a company that is just entering a Phase I study to evaluate what standards will apply universally; it's much easier to embark on this process during Phase II or Phase III. In Phase I there are some standards that can be implemented such as margins and the headers, but the data sets that will impact the hyperlinks are almost impossible to establish at that point.

CLARK. Within companies, where the sub-


SYDNEY GILMAN

If all disciplines within a company had a working knowledge of what is required as documentation for a NDA and supplied this knowledge to the final format, **WORKING TIME TO "BUILD" THE NDA WOULD BE SHORTENED SIGNIFICANTLY**.

mission process remains manual, often managers are unaware of the status of the documents being written within different functional areas. They don't know if the different groups are following the same standards or if they are even using templates. The regulatory group — regulatory affairs and regulatory operations — that has to bring all the information together doesn't have a good idea of what all the functional areas are doing. They are not able to review what is being written. Therefore they have minimal input on what is being done. An organization needs to roll out standards for the submission process. The regulatory group needs to be able to work with all the contributors in all of the functional areas who have any input to the submission document. This includes the clinical group, the preclinical group, the toxicology group, the physicians, the regulatory affairs group, the biostat group, the clinical programming group — any group that is writing summaries. Those groups need to be able to pull together and agree what the submission standards are going to be for the company.

MAKRIS. One of the biggest obstacles in the submission process is the actual drug-development process. Because the clinical phase of drug development can take between five and 10 years, the systems and standards that were in place during the initial phases of data collection and documentation will have changed. So in the end, a company is left with legacy systems, legacy databases, or legacy data that don't conform to today's submission process standards. A company may have established standards for a submission back in 1995 — having worked through all of the obstacles and adhering to the guidelines of the day — but today using that same data it would be impossible to make a submission. The biggest obstacle is going back and determining how data were collected and matching them to today's requirements.

WALKER. Companies that can establish standards and train people early on those standards and ensure adherence are the companies that will manage their submissions much more successfully.

CLARK. There are guidelines from the FDA and the General Consideration Guidance on what the minimum standards for a submission document should be, such as the font, margins, and so on. These are the absolute minimum requirements the agency needs. I have found that there are other areas, outside the minimum standards, that people have preferences about. For example, some people prefer to have headings one way, others prefer to use "refer to" instead of "reference at" — these are the preferences where a company needs to have agreed upon standards. The idea is that all of the documentation should be consistent so that when the FDA is reviewing a company's documents, the only thing that is different is the content. This agreement on consistency needs to happen early in the process to smooth the submission compilation process.

GALLE. Most companies have a certain number of templates that are sanctioned for the creation of documents. But, again, if those templates were created with only clinical-study reports in mind, they might not translate properly to what someone in the pharmacology area is doing. Or they might not translate properly for someone who is putting together an analytical method section. The error is not involving the right cross section of different technical content specialties in putting systems together.

CLEGG. One of the biggest obstacles is the integration between the document-management system and the dossier assembly and publishing tool that are available on the market. There are a few products now available that provide this level of integration. With an integrated system, users have the ability to manage the content in a compliant manner, maintaining audit-trail and signature approval information as it is placed in predefined templates, whether it's an IND or NDA — paper or electronic. As the content is gathered for the submission the regulatory-affairs group has the ability to drag and drop the content into the appropriate section of the dossier. And through the seamless integration, the dossier is then available to be published electronically.

GILMAN. Beginning with the early documents of a project, these should be formatted to meet NDA submission requirements. Companies need to ensure, before acquisition, that the system or software of choice can handle all of the required tasks, file sizes, and so on.


JAMES WALKER

TETZLAFF. The key to establishing data integrity as a core company value is to build data integrity into the design of every quality system in the company, including both commercial production as well as the facilities used for production of clinical-trial materials. Companies that intend to submit data electronically to the FDA will want to develop and implement EDC systems that ensure accuracy by eliminating the need for data transcription. A number of EDC tools are commercially available that can be installed on an enterprise-wide basis, including applications for product development facilities and clinical investigators. Such systems should provide on-screen edit checks, as well as the ability to perform automated queries and to generate reports for data from clinical trials and the production of clinical-trial materials. By applying advanced EDC solutions, companies can decrease the amount of time needed to prepare submissions and improve data accuracy compared with paper-based systems.

THE ROLE OF 21 CFR PART 11

WILLIAMS. At times, the resulting chaos and challenges to adapting to these major changes can seem a bit overwhelming. This may be even more evident to more mature organizations, which already are experiencing the inefficiencies of yesterday's processes in meeting today's regulatory demands. So how do companies prepare to weather these seas? Organizations have to reevaluate practically every aspect of product development, they have to educate themselves relative to current expectations; they have to understand current technology and critically examine its application to current processes. In short, companies have to establish a new perspective and framework that is germane to the new paradigm. Thankfully, the FDA has recognized the need for establishing a regulatory framework for transitioning from paper-based to electronic systems of information management. This regulatory framework is 21 CFR Part 11, which establishes the requirements for ensuring that proper controls are instituted to affirm that the electronic copy is exactly as the paper copy would be. Part 11 has allowed the introduction of a lot of electronic technology into the drug-development process, especially in compilation and publishing processes for generation of regulatory documents. Publishing software systems now allow the electronic compilation and publishing of regulatory submissions consisting of tens to hundreds of documents that make up investigational and marketing applications into a more user-friendly and less voluminous set of CDs. The foundation for transitioning into the electronic world afforded by 21 CFR Part 11 imparts tremendous efficiencies into handling the immense amount of data and information that comprise regulatory applications. Just eliminating handling of paper and the copying processes represents tremendous gain. In addition to the benefits afforded to publishing of regulatory documents, front-end electronic applications are emerging that will facilitate the entire documentation process surrounding clinical trials. For instance, technology such as the electronic Trial Master File (eTMF) system used by PRA allows site registration documentation to be brought in-house and processed in a totally electronic environment. Documents can be reviewed and any changes coming out of that review process are also governed electronically. In the past, those processes involved taking stacks of paper to one person; and if there was a secondary review, then the documents had to be manually passed to another person. Electronic front-end and back-end applications added to existing databases are being used to augment the document publication process of such adverse event reporting and automated production of the multiple summary tables and text required in INDs and NDAs.

> Companies are having to change the way they write the clinical study report to extract all the efficiencies out of the electronic processes. **THE FUNCTIONAL AREAS NEED TO BE BETTER EDUCATED ABOUT WHAT "SUBMISSION READY" MEANS AND WHAT THEY NEED TO DELIVER TO REGULATORS.**

TETZLAFF. By far the best way to take advantage of 21 CFR Part 11 will be to reduce the amount of time and resources for transcription of data and information into technical reports and to eliminate the manual verifications of the accuracy and completeness of data. Systems that are fully compliant with the requirements of Part 11 will provide more reliable and accurate data than manual systems that necessitate data to be transcribed/tabulated. That makes them subject to transcription errors and omissions. By eliminating potential sources of errors and omissions from manual entries, systems that are Part 11 compliant will be able to provide a higher assurance of data integrity, and project timelines can be reduced by eliminating labor intensive data verifications for accuracy and completeness. Systems that capture and store data electronically in a format that can be used to prepare summaries and reports are less prone to errors and omissions — provided the systems have been adequately validated. Because accuracy and completeness are attributes that can be quantified, the results derived from automated systems can be tested against predetermined specifications. A validated system will provide a high degree of assurance that the system is capable of consistently producing results that meet predetermined acceptance criteria.

MAKRIS. 21 CFR Part 11 introduces a whole new area of cost assessment. Take for example a biotech company that is initiating Phase I studies for a compound. A consultant might suggest to the company that it establish standards for archiving and warehousing data for a submission that might take place six years later, when we all know in Phase I there is a high risk of this drug actually not being suc-

cessful. It becomes a very fine line at which state the sponsor feels comfortable in making the investment in the infrastructure and the process of creating standards across all of its studies. The intent might be there, but it's a very business-driven decision as to what stage in the development process a company begins to implement standards that would make the submission process free of obstacles.

GILMAN. Companies need to evaluate what "systems" they currently have, what they are currently able to do, what works, and evaluate the bottlenecks and/or what they need to be able to do. Companies need to evaluate if a high-level publishing capability is what is needed or if a mid-level or entry-level system or even outsourcing would suffice, based upon

Regulatory Submissions Trends Survey 2002

A GLOBAL SURVEY ON REGULATORY SUBMISSIONS TRENDS, THE FIRST OF ITS KIND, WAS CONDUCTED BY CDC SOLUTIONS IN DECEMBER 2002 to gauge how regulatory departments are using technology today and how they plan to harness technology in the future.

Slightly more than half of the respondents came from the United States with the remainder coming from various European countries, including 11% from Germany, 8% from the United Kingdom, and 7% from Ireland.

More than three-fourths of respondents were from large pharmaceutical, medium to small pharmaceutical,biotechnology, and medical-device sectors.

The survey concentrated on three key trends: technology usage, outsourcing, and regulatory.

According to the survey respondents, 70% currently make regulatory submissions. When asked what kind of system they use for submissions:

- 37% use a paper-based system;
- 34% use a combination of paper and electronic; and
- 7% say they use an electronic system.

Within the next 12 months, 19% of respondents say they plan to move to a full electronic system while an additional 34% say they plan to make the change in more than 12 months.

More than half of respondents (58%) anticipate their use of regulatory submissions software will increase and respondents identified process improvement and compliance with 21 CFR Part 11 as the greatest benefits to using regulatory publishing software.

Almost 50% of respondents anticipate their use of outsource vendors as a whole will increase or stay the same.

The majority of respondents indicate they are either compliant with 21 CFR Part 11 or are planning to become compliant. But to become compliant, respondents believe it will impact their company's people, processes, and technologies.

TECHNOLOGY USAGE

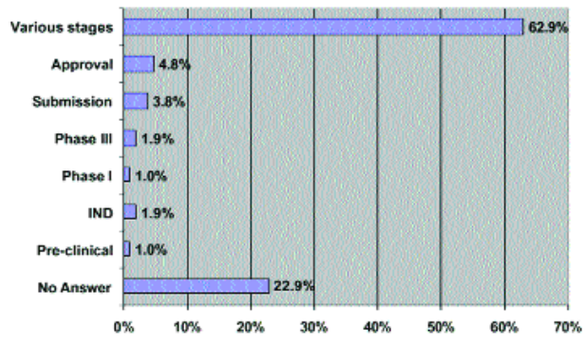
More than two-thirds of the respondents indicate that their companies already make regulatory submissions with more anticipating making submissions; the Food and Drug Administration (FDA) is the regulatory authority to which most respondents are submitting.

Technology usage is expected to increase in the next year. According to the survey, 60% of respondents say their use of regulatory submissions software will increase, and 19% believe that they will implement a full electronic submissions system within 12 months.

Respondents place high importance on electronic document management and compliance with 21 CFR Part 11. Less important, according to respondents, is being placed on regulatory information databases.

When asked about a timeframe to move to a full electronic submissions system, 19% say

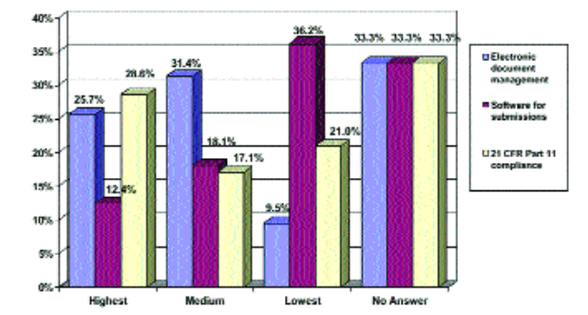
AT WHAT STAGE DO YOU BELIEVE IT IS BEST TO EMPLOY ELECTRONIC SUBMISSIONS?



More than half (50.5%) of respondents believe that it is best to employ electronic submissions software during the submissions stage and 27% say it is best during IND submissions.

Respondents could give more than one answer for this question.

HOW DO YOU RATE THE IMPORTANCE OF ELECTRONIC DOCUMENT MANAGEMENT, SOFTWARE FOR SUBMISSIONS, AND 21 CFR PART 11 COMPLIANCE?



Respondents were asked to rank in terms of importance electronic document management, software for submissions, and compliance with 21 CFR Part 11. Electronic document management was most often ranked at the highest or medium importance (57%). Compliance with 21 CFR Part 11 was next with 46% placing this at high or medium importance. Of the respondents, 30% placed software for submissions at high-medium importance. One-third of respondents chose not to answer this question.

economic mandates, anticipated number of future filings, and their level of difficulty. Companies need to predetermine what features are necessary, what will the improved features save, as well as cost. Companies need to predetermine if the regulatory department is going to be growing or will it be expected to do more work with the same resources? What will a department gain by upgrading to a new system? Then, companies need to implement a document control/data-management system that meets all the requirements of 21 CFR Part 11 such as security, audit trail, and so on. Finally, when purchasing software, companies need to make an attempt to identify and purchase software that is readily accepted and validated. The same would hold true for "systems." For example, many document control manufacturers provide — for an additional cost — validation packages that comply with 21 CFR Part 11.

they will make the move within 12 months. An additional 34% of respondents anticipate that they will make the move but it will be more than a year.

OUTSOURCING TRENDS

While almost one-fourth of the survey's respondents say they do not use outsource vendors, most companies responding say they do outsource some activities, and nearly half expect that their use of outsource vendors will increase or stay the same.

Clinical research tops the list of activities that survey respondents outsource (35%). One-fourth of respondents (26%) say they do not outsource. While, 14% say they outsource submissions.

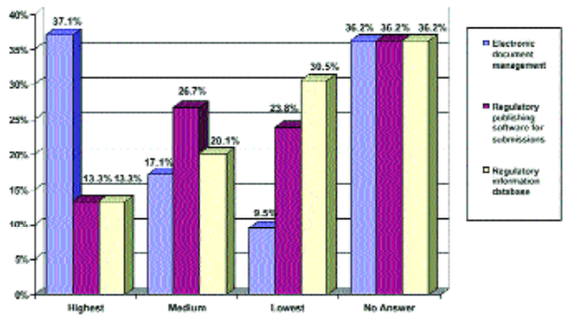
REGULATORY TRENDS

The majority of respondents indicate they are either compliant with 21 CFR Part 11 or are planning to become compliant. But to become compliant, respondents believe it will impact their company's people, processes, and technologies.

Regarding their plans to migrate the submission process to the electronic common technical document (eCTD), one-fifth of respondents say they are uncertain while more than one-third say they do currently have plans.

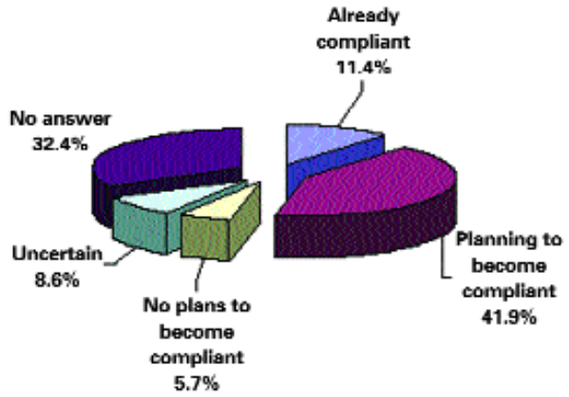
More than one-third, though, believe the eCTD will require a change in their company's submissions process within the next 18 months.

HOW DO YOU RATE THE IMPORTANCE OF ELECTRONIC DOCUMENT MANAGEMENT, REGULATORY PUBLISHING SOFTWARE, AND REGULATORY INFORMATION DATABASES?



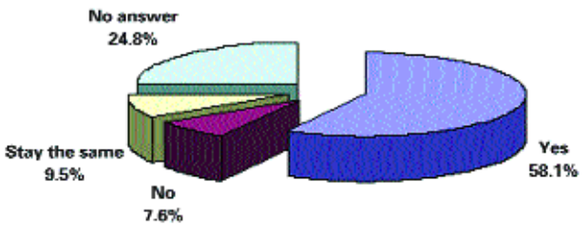
When asked how they rank the importance of electronic document management, regulatory publishing software for submissions, and a regulatory information database, electronic document management was most often listed at a high or medium importance (54%) and regulatory software was second with 40% listing this at high or medium importance. Of the respondents, 33% listed regulatory information database as high or medium importance.

DO YOU HAVE PLANS TO BECOME COMPLIANT WITH 21 CFR PART 11?



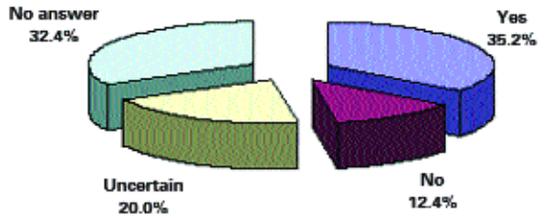
More than 50% of respondents are either already compliant (11%) or planning to become compliant (42%) with 21 CFR Part 11.

WILL YOUR USE OF REGULATORY SUBMISSIONS SOFTWARE INCREASE?



Overwhelmingly, survey respondents anticipate their use of regulatory submissions software will increase (58%).

DO YOU HAVE PLANS TO MIGRATE THE SUBMISSION PROCESS TO THE ECTD?



More than one-third of respondents (35%) say they have plans to migrate their submissions process to the eCTD. Another 20% were uncertain about plans, and 12% said they do not currently have plans to migrate to eCTD.

Source: CDC Solutions Ltd. Report, January 2003

Note: CDC distributed more than 5,000 surveys to professionals in the regulatory departments of pharmaceutical, biotechnology, medical device, and contract research organizations (CRO). The above text is a sample of the information provided in the report. The majority of the 105 survey responses were collected electronically. Results were calculated and rounded to the nearest tenth of a percent. All responses were included in the results, and each question depicts answers as they were given by survey respondents.


JASON CLEGG

In an electronic system, ad hoc changes to the submission can be done quite easily and the submission is automatically updated. **IF TWO OR THREE DAYS CAN BE CUT FROM THE PRODUCT COMMERCIALIZATION PROCESS IT COULD POTENTIALLY SAVE THE SPONSOR MILLIONS OF DOLLARS.**

OVERCOMING RESISTANCE TO CHANGE

CLEGG. The problem with paper is that there is so much manual effort involved in collecting the documentation, organizing the documentation, and getting documentation approved. Whereas with an electronic system, there is the ability — with the point and click of a mouse — to create the appropriate dossier structure. And as content is created, there is the ability to populate that dossier faster compared with paper assembly. Additionally, there is a complete audit trail of who did what to the document, what changes were made, and so on. Part 11 made people look at the methods they were using to control a document and the methods they were using for document approvals. There is an advantage when it comes to time and effort by creating a submission electronically.

TETZLAFF. The reasons that many companies have resisted the migration from manual paper-based systems to EDC systems are varied. First, there is management's reluctance to change the established documentation practices used by clinical investigators. Second, there is the perception that there will be additional costs for the development, or purchase, of new EDC systems. Third, implementing EDC technologies may result in extra pressures to design enterprise-wide functionality at much earlier phases in the development life cycle, compared with paper-based systems where documentation design may be delayed until later phases of the development project. And fourth, management is reticent to be accountable for a change that is viewed as high risk, with the potential to delay product approval and/or unpredictable outcome. For example, clinical investigators may resist changing from established processes to EDC systems unless they see a decided cost advantage — time/resources — for their studies. Investigators may resist the learning curve needed to change their methods of data capture. Many departments may not have capital budgets to allow for the up-front costs associated with the purchase of a commercial product, and hence they rely on manual systems, even if the systems are known to be less efficient and probably more expensive over time. Other companies are reluctant to implement new technologies in the middle of a key new drug-development project for fear of having an unsuccessful outcome that potentially could delay NDA submission and/or product launch. Many companies are loath to take risks with the introduction of new technologies or applications unless they are confident that there is almost absolute certainty of approval by the FDA. Some managers resist the change to EDC because they do not want to be held accountable for the decision to migrate to EDC in the event that the change results in an unexpected delay in product approvals or product launch. They take a more conservative approach based on the perception that their careers may be at greater risk based on uncertain or less predictable outcomes.

MAKRIS. With regard to EDC, now that we are dealing with the fourth generation of systems, the primary reason for slow adoption is user acceptance. The individual who enters the data into the system needs to be well-trained. But most times this function happens at the site and this is not their primary role or function. Unless we, as an industry, address this, I am fearful that we will have yet another generation of technology.

GILMAN. The overall total costs — money, training, time to implement, validation — are all unknown. The task of validation can be overwhelming and most companies don't have the in-house expertise to guide them through this process or even have an understanding of how to approach/begin the process. 21 CFR Part 11 is only a couple of pages long, but it offers very little help in understanding or satisfying the requirements.

CLEGG. The key to overcoming resistance involves more than the issue of being regulatory compliant; electronic systems must enhance business processes overall by implementing quickly, improving efficiency, and decreasing time to market. There has to be an argument for the company to move to an electronic environment, and the way to do that is by demonstrating return on investment and saving time and money on the submission process. Because the tools for automating the electronic submission process have only been around for a few years, many people still are unfamiliar with their available options and they are still trying to educate themselves about the benefits. One of the problems of realizing the benefits is that the large enterprise document management installations in the past have not been smooth or easy. There have been long implementation and validation times and therefore, it's often taken a while to realize a return on investment.

WORKING WITH REGULATORS

GALLE. Any content that is created today without CTD in mind is instant legacy. There's no reason not to create content according to ICH guidelines. When companies make the decision — and no decision is a decision — not to change their process and continue to create content as they have in the past, they are creating instant legacy and creating problems for themselves down the road. We are strong advocates that companies need to take advantage of the guidelines that ICH has put together and use those to create the content for every product, which translates into any document that may end up in a regulatory filing.

MAKRIS. There are many ways in which companies can have better relations with the FDA. Each sponsor should take advantage of having contact with all the reviewers at the FDA — when I say all I also mean the statistical reviewers who often are overlooked. Sponsors fear that the more detailed discussions they

have with the agency, the more committed they will need to be in their requests. Companies fear that the more they expose themselves, or the more information about the clinical development plan they provide for review, the more likely that the FDA may make recommendations that they then would have to follow. Therefore, many companies prefer not to have contact until the final submission is made. This is a mistake; companies should not go to a pre-NDA meeting and say here is what we are planning to do, and we'll see you again at the end.

WILLIAMS. Yet, even with the introduction of the 21 CFR framework, there remains a lot of uncertainty both in the industry and at the FDA. This uncertainty stems from the tremendous cost of shifting to a new paradigm and questions relative to how deep companies need to dig to lay the foundation for this shift. In a general sense, Part 11 could control every aspect of computerized processes that would generate a paper copy. Questions relative to the impact of Part 11 on current processes and systems and the extent to which the regulations would be enforced, only raised the level of anxiety and uncertainty within industry. Having worked at the FDA for a six-year period, during which time Part 11 came out in 1997, I know that divisional differences within the agency in the application of regulations and guidances probably contributed to the widely varied interpretations that were promulgated following its release. The newly released version didn't really change the requirements for compliance, but more narrowly defined the scope of its regulatory application. In the new guidance full compliance with all requirements of Part 11 is now limited to documents that are truly generated, managed, and archived electronically. This more narrowly defined scope will eliminate much of the varied interpretations that were circulating. However, there remains a lot of debate on exactly how and what type of technology would best implement requirements, such as electronic signatures and computer-validation processes. Thus, we again find ourselves in the middle of a paradigm shift with multiple products designed to address Part 11 requirements, but no one seems quite assured that all the proper controls are instituted and systems are validated and that there are measures that can address all the regulatory requirements.


SHANNON WILLIAMS

PHARMACEUTICAL PRODUCT DEVELOPMENT CURRENTLY IS EXPERIENCING A PARADIGM SHIFT from a paper-based foundation to an electronic one. And anytime there is a major shift in paradigm, there is a lot of uncertainty.

FERRIS. Many of the challenges that companies face with regard to electronic safety submissions carry over into new drug applications. Essentially, this is the same type of project where it is a process that has been done on paper or other physical media until very recently. This is a moving target; there are some guidelines set forth, in the case of E2B by the ICH, but there also are variations as to how each regulatory authority digests that information. In many cases, the authorities have come up with extra requirements or ways in which they need companies to submit information. Managing these different requirements is the most overwhelming aspect of the submission process, according to customers I speak with. It would be great if companies could implement a technology, create the reports, and send them in the same way to every single regulatory authority, but that's not the case.

WILLIAMS. The shift from a paper-based to an electronic environment is occurring in concert with other regulatory changes, such as the transition of marketing application formats to the ICH's CTD format and now to the eCTD format. Other technologies such as extensible markup language (XML), a new data qualifying components of the eCTD also are emerging. And although XML has been used in industry and business for a while, its use in pharmaceutical product development has been fairly limited. Thus, the assimilation and integration of emerging technologies such as XML, serve to further complicate the transition from a paper-based to electronic environment. When a company goes to an electronic environment and sets up the framework there is an enormous amount of detail in terms of standardization that have to be implemented so that everyone can adhere to those standards. Currently, we are faced with implementing new technologies lacking many of these standards. And although organizations such as the ICH and CDISC have put forth efforts in setting those standards, processes for standardizing XML tags for data in the eCTD and EDC environments still haven't been fully ironed out.

GALLE. There is a lot less wiggle room for how information is to be presented with the CTD. The guidelines have been circumscribed down to a granular level as to what information is supposed to be where in an application. The art of how to organize information within a submission or a study report has diminished. There now should be a lot more consistency. That might be hard for technical writers to accept, because they might believe, right or wrong, that the way they did things historically in organizing and presenting information was the best way. If companies are not investing in the training to bring people on board there will be issues during this transition — and it will be more difficult than it needs to be. Changing processes to comply with CTD is the largest paradigm shift that we've seen in some time, and in fact, it's a larger shift than moving from paper to electronic.

FERRIS. Many of the regulatory authorities have small differences, but differences nonetheless, in exactly how they want submissions done. It's a process of having to understand and meet different requirements for each regulatory authority and making sure that each is sent the right report. Not only do companies have to put in place new technology and learn how to manage the system, they also have to get their arms around how to build and send the files to each authority. There are many challenges and the learning curve is big. ✦

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