

PDF as a Standard for Pharmaceutical Electronic Submissions

Pharmaceutical, biotechnology, and medical products companies are faced with the enormous challenge of developing and marketing new products in a highly regulated environment. Companies are required to submit thousands of pages of documentation as part of the regulatory review process for new drug and medical products. While companies are under pressure to accelerate time-to-market and reduce expenses, the nature of the regulated environment tends to slow down product development and increase development costs.

A key to increasing time-to-market and containing costs is the electronic submittal of information to the regulatory agencies. Regulatory agencies worldwide have envisioned integrated systems to support the full range of regulatory functions, from discovery through post-marketing surveillance. In the United States, the Food and Drug Administration (FDA) is supporting this effort. Internationally, there are initiatives from the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH).

The adoption of the Portable Document Format (PDF) as a preferred submission format by worldwide regulatory agencies has hastened the acceptance of electronic submissions and has allowed many corporations to save both time and money. Documents created in any application—even hard copies, microfilm, forms, and medical images—can be converted to this universal file format. PDF files can be tracked and archived through the development process. Reviewers can view and mark them up on-screen. Once the preparatory work is complete, a comprehensive, compiled submission can be created and submitted electronically to the regulatory agency.

With the total time-to-market for a new drug averaging 10 to 15 years and the average cost for bringing a new drug to the clinical trial stage now a staggering US\$802 million*, it is essential to get to market as quickly as possible. Electronic submittal of applications can help every organization achieve this goal.

Today's Regulatory Arena

The need to streamline electronic submissions is reflected in government initiatives worldwide. Where lives and health are at stake, the need for streamlining regulatory practices is essential. Every major regulatory region—North America, Europe, and Asia—has its own requirements for the organization of electronic submittals of new drug applications. In Japan, the applicants must prepare the GAIYO, which organizes and presents a summary of the technical information. In Europe, expert reports and tabulated summaries are required, and written summaries are recommended. The FDA has guidance regarding the format and content of a new drug application (NDA). An NDA usually represents seven years of research and development plus an additional two years of review and approval.

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* Source: "How New Drugs Move through the Development and Approval Process," Tufts Center for the Study of Drug Development (2001).

Through the ICH, considerable agreement has been achieved among the three regions regarding the technical requirements for the registration of pharmaceuticals for human use. ICH is currently working on the Common Technical Document and the Electronic Common Technical Document, which will be accepted in all three regions.

History

The pharmaceuticals industry is well known for its conservative approach to the adoption of new technology. The extensive regulatory requirements that corporations must face to validate the accuracy and reliability of systems used throughout the drug product life cycle have caused the industry to be cautious about implementing new software concepts and tools.

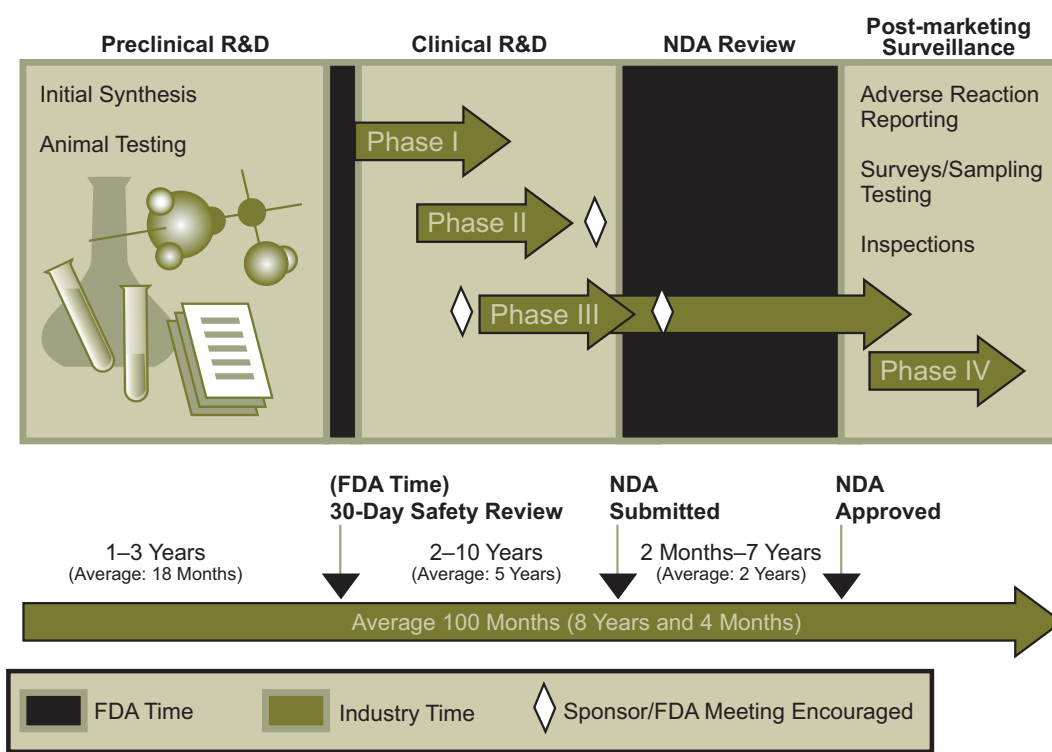
Such has been the case in the adoption of automated electronic publishing systems for regulatory submissions. Typically, a paper-based drug regulatory submission involved a profusion of documents that were prepared with virtually no support of automated content management or electronic publishing systems. Individual documents were organized in folders on a network file system. After printing, headers and footers were applied manually, and pages were hand-assembled into a myriad of binders. Electronic solutions were being widely piloted, but production systems designed to publish fully electronic regulatory submissions have only become common practice in the last few years.

In the United States, it is the FDA's goal to establish a process for submitting electronic applications that creates minimal additional work for sponsors and reviewers, provides maximal flexibility for sponsors and reviewers, establishes consistency in information transfer requirements across the FDA, and expedites the review process. In 1998, the Center for Drug Evaluation and Research (CDER) issued draft guidance for an electronic NDA, and the Center for Biologics Evaluation and Research (CBER) issued several draft guidances, including "Guidance for Industry: Electronic Submissions of a Biologics License Application (BLA)" and "Guidance for Industry: Electronic Submissions of Case Report Forms (CRFs); Case Report Tabulations (CRTs); and Data to the Center for Biologics Evaluation and Research."

A breakthrough came in 1999. CDER and CBER established joint guidance for electronic submissions identifying PDF as the primary electronic submission format. It was easy to create at a low cost and could mimic the type of paper submissions that the agency was accustomed to. Recently, the FDA has supported the use of the Electronic Common Technical Document for submittals. It prescribes a common structure using both PDF and XML.

Drug Development Process

The development of a new drug typically occurs over an 8- to 12-year period and consists of three distinct stages: drug discovery, drug development, and drug marketing. A new drug evolves from hard-science research to product development and testing, and eventually to marketing. During this process, hundreds of people throughout the corporate enterprise are creating or capturing millions of pages of supporting documentation. When this information needs to be turned over to the appropriate regulatory agency for review, submitting it on paper is an enormous task. This amount of paperwork is not only expensive to transport and store but also time-consuming for reviewers to sort through, review, and analyze.



Pharmaceutical companies that apply technology to this problem can gain a competitive advantage. By managing the disparate documents and automating the collaborative efforts required for electronic submissions, companies can save enormously on labor-intensive tasks such as manually collating, copying, and distributing paper.

Regulatory agencies around the world are also under pressure to streamline the submissions process. Every major country in the world has adopted aggressive e-government deadlines, mandating agencies to shift from paper-based processes to electronic processes. The public and the pharmaceutical companies pressure the agencies to be more proactive and responsive. The necessary scientific process of drug or device approval can be held back because of the enormity of the task, especially when dealing with a submission that is on paper. Regulatory agencies have responded by:

- Looking for and encouraging ways to reduce or eliminate the costs associated with processing, moving, and storing paper
- Streamlining the process of finding information on the submission internally, thus saving time
- Offering faster support and response time to agency questions
- Participating in international harmonization efforts

PDF Description

PDF is a publicly available specification. It is used by standards organizations to create open standards and is the de facto standard for digital documents with more than 20 million PDF files available on the public Internet today. Being a publicly available standard means that although Adobe created it and advances the specification through subsequent releases, all the information about the nature of PDF is made available publicly.

Many people confuse PDF, the publicly available file format specification, with Adobe® Acrobat®, the proprietary software that Adobe sells to create, view, and enhance PDF documents. They are completely distinct. Moreover, there are more than 1,800 vendors that offer PDF-based solutions, including PDF creation, plug-ins, consulting, training, and support. And although free Adobe Reader® software is installed on virtually every Internet-connected computer today, some organizations have chosen to write their own PDF reader software as well.

The PDF specification was first published in 1993. Since then, updated versions of the specification continue to be available from Adobe via the World Wide Web (<http://partners.adobe.com/asn/developer/acrosdk/docs.html>). The current version at the date of this publication is version 1.4. All of the revisions for which specifications have been published are backward compatible, that is, if you can read PDF 1.4, you can also read PDF 1.3, PDF 1.2, and so forth.

The actual name *Portable Document Format* was coined to illustrate that a file conforming to this specification could be viewed and printed on any platform—UNIX®, Mac OS, Microsoft® Windows®, and several mobile devices as well—with the same fidelity. A PDF document is the same for any of these platforms. It consists of a sequence of pages with each page including the text, font specifications, margins, layout, graphical elements, and background and text colors. This is so that the PDF file can be imaged accurately for the screen and the printing device. It can also include other items such as metadata, hyperlinks, digital signatures, and form fields.

An excellent source for information regarding PDF products, tools, and third-party vendors can be found at www.pdfzone.com and at www.pdfplanet.com. Many of these third-party vendors have specific products targeted at the pharmaceutical/medical device industry. They have used the specific guidance provided by regulatory agencies on the format of an electronic submission to create productivity tools. Who wouldn't want to automate the creation of bookmarks and hyperlinks throughout an NDA?

PDF as a Standard

Standards that are endorsed by a standards body such as the International Organization for Standardization (ISO) or the American National Standards Institute (ANSI) are referred to as de jure standards. On the other hand, data format standards that become a standard by sheer volume of usage and acceptance by users are called de facto standards. De jure standards take a long time to develop and must be approved by every organization that is a member of the standards organization with interests in the area covered. These standards bodies generally include industry members, technology developers, engineers, and specifications experts. An example of a de jure standard is PDF/X, an ISO standard developed to facilitate content exchange for prepress printing. Additional de jure standards efforts are under development today, including PDF/A for archiving digital documents and PDF/IS for Internet fax standards.

De facto standards spring up in response to an immediate industry need. They gain in use and popularity through market dictates. Adobe PostScript® and PDF are both examples of de facto standards. The usefulness of these formats has been recognized across governments and industry. For instance, there are 2 million PDF files on U.S. government Web sites alone, and to date, over 500 million PDF files have been downloaded from the U.S. Internal Revenue Service Web site.

Mandated standards include those that are either regulated or suggested for compatibility. The FDA's regulations for the submission of NDAs are an example of mandated standards. These NDAs can be submitted electronically, and the FDA requests that the document portion be submitted in PDF with very specific attributes, such as bookmarks and hyperlinks. In fact, the FDA publishes guidance on the subject of acceptable electronic formats (www.fda.gov/cder/guidance/).

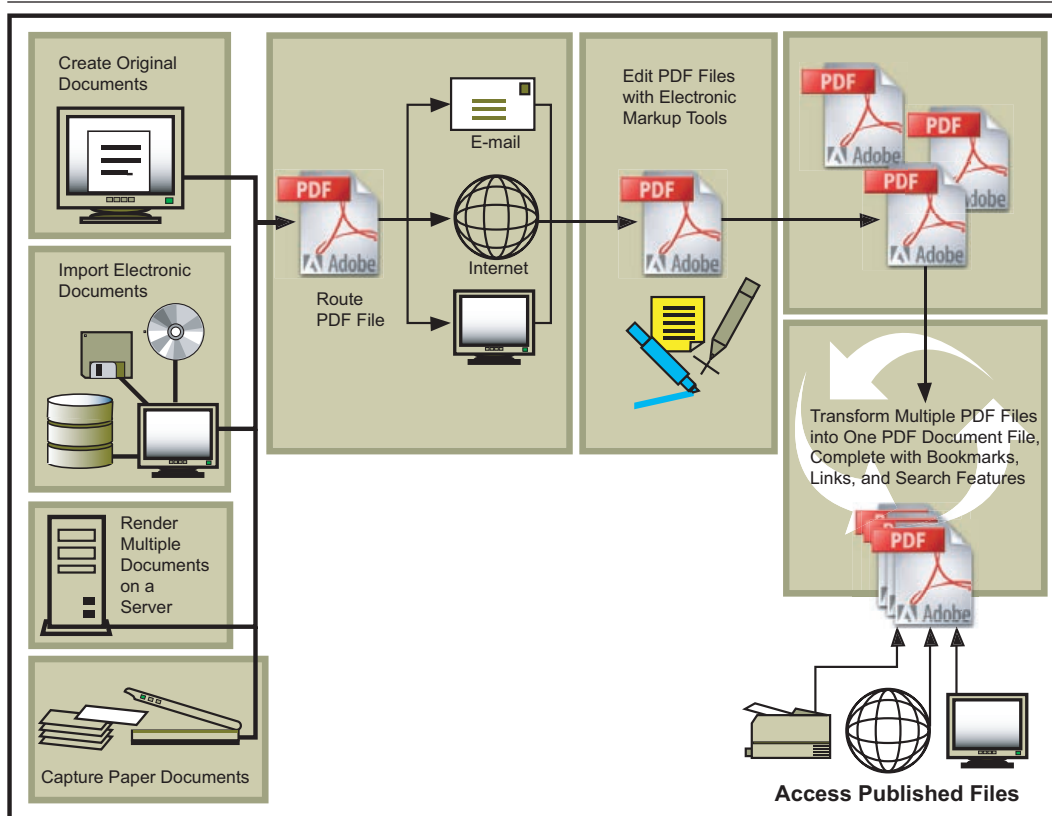
Complementary Technologies

A complex interaction of corporate employees, content, research, technology, and overriding regulations forms the basis for many automated systems in the pharmaceutical arena. Electronic submissions require two basic components: the ability to create the documents electronically and the ability to publish them either in paper or electronic format. Creation of the documents used to be as simple as typing into a Microsoft Word file and having one person collect all of the finished files and assemble them into a submission. Many regulatory agencies now expect versioning, audit trails, and better security in the creation process. In addition, electronic formatting not only means fonts and page numbers but also hypertext linking, table of contents generation for PDF, and specific file and directory naming conventions. To comply with all of these requirements, a document management system is necessary.

A document management system provides a container that maintains the documents. Documents are still created in their native file formats: Microsoft Word, Excel, PowerPoint, and so forth. The document management system automatically tracks who made what change and when. It also prevents users from saving over previous copies and obscuring changes. Two systems that have been used by many pharmaceutical companies are Documentum (www.documentum.com) and CoreDossier (www.liquent.com). They play different roles but usually work in concert to produce an electronic submission in PDF. There has been a long history of integration and cooperation between Adobe and these companies.

PDF-Creation Methods for Electronic Submissions

PDF has solved many of the electronic submission problems by offering an easy way for all individuals throughout the enterprise to share information and create a comprehensive submission. With advanced networks and infrastructure already in place, organizations can cohesively create files and assemble submissions in record time. Even paper and microfilm can be converted into PDF.



Instead of printing to paper, all documents that are part of a submission are converted to PDF. This can be done with the Adobe Acrobat software family, including Acrobat Capture[®] 3.0 software for converting paper to electronic PDF files. Once all parts and pieces of a submission are converted to PDF, they are assembled in the manner that the regulatory guidance dictates. This usually means folders and subfolders, all with specific names. Using the document merge functions in Adobe Acrobat 5.0 software, you can turn multiple files, authored in separate applications, into PDF files. This is essential to create a compliant submission. Specific tables of contents, hyperlinks, and bookmarks are then created in the PDF files. This allows reviewers to quickly navigate a huge submission.

Once the submission is created, Acrobat can be used to create a full-text index of the submission. This allows both submitters and reviewers to search for keywords and phrases across all the files of the submission. This provides a powerful tool, both for the submitting and reviewing organizations.

Another benefit of using PDF is realized when documents are being prepared for the submission. Using the annotation tools offered in the Acrobat product, quality assurance personnel across the organization can provide their markups directly on the electronic file. This means that nothing will get lost and all comments are recorded electronically.

A global library of the electronic submissions is powerful, both to the submitting organization and to the regulatory organization. By standardizing on PDF, the inclusion of digital signature technology is possible. Combined with document management products, the legacy of the submittal can be maintained.

FDA Case Study

Pharmaceutical and medical device manufacturers are not the only organizations to benefit from a process that includes electronic submissions. The regulatory agencies also benefit. Benefits for a regulatory agency that relies on electronic submissions include:

- Cost savings on processing, moving, and storing paper
- Time savings in finding needed information dispersed within the organization
- Faster support to constituents regarding responses to agency questions
- Ability to collaborate and work with team members in different geographic locations

Each year, the FDA receives many submissions, including more than 100 original NDAs from pharmaceutical companies that want to introduce new drugs, market a drug for a different therapeutic purpose, or change dosage recommendations.

The FDA currently reviews NDAs more efficiently and at a lower cost with Adobe Acrobat software and PDF. The FDA employs 700 reviewers to review NDAs. The NDAs can contain as many as 1,000 volumes of 300 pages each and must be submitted in triplicate. When NDAs are submitted in PDF instead of on paper, reviewers have access to fully searchable electronic files that are easier to locate and distribute. Plus, the costs to the agency of storing these documents are reduced substantially. And when used with features in Acrobat, including rich annotation tools and the ability to copy charts from PDF files to Microsoft Word or Excel or to compare versions of PDF files side by side, PDF can help accelerate the decision to approve or not approve an NDA.

Since 1997, the year that the FDA first allowed pharmaceutical companies to submit NDAs in PDF, the agency has received more than 80 such submissions containing in total the equivalent of more than 7 million printed pages. Pharmaceutical companies may find it an economic advantage to submit NDAs electronically. In some cases, they can eliminate days or weeks of printing and validating nearly

a million pages and reduce photocopying and shipping costs substantially. What's more, market-leading drugs can earn US\$1 million a day—thus, receiving approval to introduce a new drug several days earlier impacts the bottom line.

For the FDA, the most noticeable benefits of PDF files are a dramatic reduction in storage space and greater efficiency for reviewers. A single NDA can contain hundreds of thousands of pages, and reviewers often work on as many as five NDAs at a time. The FDA stores paper-based NDAs in multiple document rooms across its campus. When reviewers have questions about specific studies, they have to request that a paper-copy volume be pulled from a document room. Obtaining a single file can take a day or more—and reviewers might easily request dozens of files during the course of a review. In contrast, NDAs submitted in PDF are stored on a central server so that reviewers can access them instantly via the corporate server or intranet. By enabling staff to immediately find answers to questions, PDF speeds review.

To take full advantage of the electronic format, the FDA provides guidance for submitting NDAs as PDF files. For example, the PDF files should include bookmarks and hypertext links to table of contents entries. And, since PDF files are searchable, reviewer can do full-text searches across multiple documents. When reviewers can quickly find the information they need, the service and effectiveness of the government agency is improved. Other specific guidance can be found in “Guidance for Industry: Archiving Submissions in Electronic Format—NDAs” (www.fda.gov/cder/guidance/index.htm) on the FDA's Web site.

The eCTD—Electronic Common Technical Document

The structure of an electronic submission consists of both the content files and file-level navigation aids. There are usually standards for file names and folder structure. In addition, a standard table of contents is usually provided with both bookmarks and hyperlinks within and between documents. The electronic submission standard has usually varied depending on the regulatory agency.

To move standards forward in an international environment, the ICH held its inaugural meeting in Brussels in 1990. There were representatives from regulatory agencies and industry associations of Europe, Japan, and the United States. The aim of this organization was to ensure that high-quality, safe, and effective medicines are developed and registered in the most efficient and cost-effective manner. These activities are pursued in the interest of the consumer and public health to prevent unnecessary duplication of clinical trials.

As part of the topics they are working on, the ICH M4 Expert Working Group (EWG) has defined the Common Technical Document (CTD), and along with it, the specification for the Electronic Common Technical Document (eCTD). The eCTD is defined as an interface for industry to agency transfer of regulatory information while taking into consideration the facilitation of the creation, review, lifecycle management, and archival of the electronic submission. The eCTD specification lists the criteria that will make an electronic submission technically valid. The focus of the specification is to provide the ability to transfer the registration application electronically from industry to a regulatory authority.

The primary focus of the eCTD is to provide a data interchange message between the industry and agencies. The industry initiates the process by creating the initial submission. Throughout the product's lifecycle, additional information will be submitted to update or modify the information contained in the initial submission, for example, supplement, amendment, and variation. The overall architecture of the eCTD is designed to provide a commonly agreed upon submission structure that imposes minimal restriction to the industry and agencies.

The philosophy of the eCTD is to use open standards. Open standards and de facto standards are appropriate for eCTD. One requirement is that the formats of the submissions should be readable at least for as long as it is needed for the regulatory process. This process could be as long as 50 years. Common formats that can be included in an eCTD submission are PDF and XML.

FOR MORE INFORMATION
For more information
on the eCTD please see
www.ich.org.

For organizations currently providing electronic submissions, PDF is the most logical to use in a mixed authoring environment. Certain data may be better represented as XML data, but documents are always better represented in PDF.

The Future of Electronic Submissions and the Role of PDF

Electronic submission to a regulatory agency is just one part of the drug or device development process. If, throughout the years of discovery, information can be created and stored in a file format that easily becomes part of an ultimate submission, time frames can be compressed. There are efforts to automate the collection of clinical trial information directly into PDF forms. No final conversion of PDF is necessary—the PDF file is created as part of the drug discovery process.

Rather than training everyone in their organization to be electronic publishers, other groups are creating databases for easy input of information throughout the drug development process. These systems automatically publish the information to a PDF file with all of the hyperlinks already established. By streamlining the process and allowing employees to concentrate on the science, the discovery process is more efficient.

All of these efforts are available today. Your organization can start saving time and money by adopting standards that support electronic submissions to your regulatory agencies.

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