

Ten Rules for Drug Regulatory Submissions

INTRODUCTION

The drug discovery, development, and commercialization process is marked by a number of important milestones. Some of these key points are delineated by scientific observations; some by legal issuance of patents; some by marketing events. But most process milestones seem to involve the submission to, and approval by, the FDA. The granting of permission to conduct clinical studies [the Investigational New Drug Application (IND) approval], the New Drug Application (NDA), which carries permission to market, and the interim steps leading to these major approvals stand out as the most important steps in the process and are tracked by investors, stock analysts, and the industry.

Each major and minor regulatory approval step is characterized by a submission, a regulatory review, and a decision. When that decision is contrary to expectations, it may be followed by a revision and, in rare cases, an appeal.

This process can be intimidating, particularly for the inexperienced regulatory professional charged with preparing a major regulatory submission. A significant chapter in the company's history depends upon the success of the submission. The result can make or break a career. And altruistically, the result can seem to determine if large numbers of patients or potential patients receive life-changing medication.

While the stakes may seem overwhelming and while some companies may maximize the pressure, the reality is much less threatening. While the FDA has an important safety role that results in barriers blocking drug approval until strong evidence is presented, the Agency has a balancing responsibility to provide the public with access to safe drug products. As a result, regulatory professionals inside the FDA are prepared to assist in the process with guidance documents, controlled conferences, and (often) informal advice.

Think of the submissions process as a major exam but one for which you have the questions in advance, can use your notes, and—on hopefully rare occasions—can retake the test if necessary.

To try and explain the process and to minimize those rare retake necessities, here are 10 summary rules for regulatory submissions.

TEN RULES

1. **Seek guidance.** Most things in life are easier the second time around; regulatory submissions are no exception. The first time you file an IND, orphan-drug application, or NDA can be confusing and intimidating. By the time you have filed your second or third submission, though, the process begins to approach the routine. Of course, everything you do has to be accomplished for a first time, but you can minimize that inexperience by seeking guidance from others. In effect, partner your first time with someone who has experience and can advise you.

One source of that advice is the FDA itself. There are formal FDA meetings, which require a written meeting request and briefing book (see Chapters 2 and 3), most appropriate before development and submission of an IND or an NDA. Less formally, FDA spokespersons often make presentations at local and national conferences. Their presentations are often available on the FDA Web site (<http://www.fda.gov>) as well as through the specific conference. Finally, some individuals from the FDA will respond directly to telephone or e-mail questions. All three of these sources can be effective information conduits and can help build strong contracts and relationships within the FDA.

If circumstances exclude the possibility of FDA advice, or if you want to hedge your bets with additional assistance, consider the use of a consulting group. It is possible, of course, to use a consultant to completely and independently prepare a submission. Such a strategy may be tempting for a one-time submission but carries a risk: When your company makes a submission, it assumes full responsibility and liability for the content, regardless of who prepared it. It is much safer and generally better for long-term corporate information culture growth to use a consulting group as guidance and assistance in preparing the submission. Let the consulting group provide help with format, recommendations for wording, the publishing and delivery services that may be onerous, and even an initial draft for review. But make certain that the final draft is a result of your company's careful revisions and acceptance. Fine-tune the document, assume responsibility, and learn the process to streamline the next submission, with or without outside assistance.

Finally, make certain that your first effort and all submissions are team affairs. Do not put all the responsibility on the director of regulatory affairs, although that person may ultimately pull together the effort, sign the submission, and lead the team. Involve input from Quality

Assurance (QA), Clinical, Marketing, and all other parts of the organization. In-house experience and diverse expertise will allow you to prevent or solve problems when they arise.

2. **Focus on format (in addition to content).** The first hurdle your submission faces is generally a format review: Until an administrative review indicates that the submission is complete and appropriately formatted, no further review can take place. So while content may be most important, do not neglect the importance of proper organization, pagination, referencing, headings, bibliography, and other formatting requirements.

These formatting issues vary from one submission type to another and sometimes from one submission recipient to another. A CNS review team may have different criteria or preferences from a Metabolic team; INDs have different requirements than orphan applications. As above (1), get some guidance and follow the preferred format.

The widest difference between FDA groups and submission types is in referencing preferences. Some groups recommend numerical referencing, tying to a numbered bibliography. Others use the American Psychological Association editorial style (author name, date), linked to an alphabetical bibliography. Most applications and most teams require that actual copies of the reference be included in the submission. Barring other statements of formatting, the default is a numerical list of articles (text copies included), with numbered references to those articles inserted in the body of the submission text.

Some submissions require two copies; some three; some even more exact duplicates. Check the submission guidance documents included here in each chapter for the specific requirements.

Cover letters are required for most submissions. Every cover letter should be dated, should carry a reference line (referring by number, IND, or other submission reference if available), and should contain complete contact information for a company spokesperson (see 7), including company name, address, contact name, title, telephone numbers, and e-mail address.

Formatting problems will delay your application and may affect the reputation and impression you are working to build. Checking the specific requirements and preferences of the group to which you are submitting can make this much easier. While content is principal, do not neglect the submission format.

3. **Document everything.** A major submission may take weeks—sometimes even months—to assemble. During that time, the writing team reviews and revises draft after draft.

When the same material is reviewed over and over, there is a natural tendency to begin subconsciously thinking of some statements as self-obvious and hence not needing documentary support. The result may

be a submission in which some key issues and assumptions are not sufficiently referenced, weakening the entire document.

To avoid the problem, identify all claims and assumptions in the first draft and have a different, independent reviewer (presumably from QA) periodically reexamine to make certain that all important points are appropriately referenced. That independence can overcome the problem even as the reviewer serves as a gadfly, challenging any controversial or unsupported assumptions.

Incidentally, most FDA submissions permit unpublished as well as published references. Supporting letters, studies not yet in print, copies of speeches and papers, and other unpublished references can be included. Refer as with any other document and include a copy in the reference section.

Web site information can also be included; reference to include the specific site and page and the date of review. And, again, include a printed copy of the site page in the reference materials.

When in doubt, remember that it is better to have too much than too little documentation. Every reference is potentially adding credibility to your submission.

4. **Self-regulate.** The FDA considers the pharmaceutical industry to be self-regulated; FDA people perceive their job as checking that you have appropriately self-regulated. That is why a technical process, even if appropriate and successful, is considered inadequate if lacking a validation and QA or control review. The double-check, self-regulation step is always required.

Counting on the FDA as your primary submission reviewer is as inappropriate as neglecting QA on the production line on the assumption that a visit from FDA investigators will serve the purpose. In any FDA submission, your QA group has an important role well beyond a proofing function.

Each of the submission documents described in this book includes two checklists. The first is a checklist intended to assist in the preparation of the document; it outlines the requirements, organizational structure, and format. The second is a checklist derived from the FDA's review and guidance documents, discussions with FDA reviewers, and with professionals experienced in the development of type submissions. It is intended to be a checklist that might be used by the FDA reviewer of the final submissions document (in many cases, these checklists have been adopted by FDA personnel and are in actual use).

The FDA Review Checklists can be used by your internal QA team to self-regulate. Acting as FDA reviewers, they can confirm that your submission conforms to all format, content, and support requirements. And, of course, should the QA team find a weakness, you can correct and rereview prior to actual submission.

Self-regulation through an appropriate QA review allows your company to take control of the process and to assume appropriate responsibility.

5. **Examine electronic submission options.** Most FDA submissions can be made manually (paper) or electronically. Obviously, the electronic submission process is more efficient, particularly when delivering large documents (INDs routinely run over 5,000 pages; NDAs may be even larger). However, there are some additional considerations.

Electronic submission standards are evolving and may not be clearly established for all FDA groups and divisions. The common electronic submission gateway (ESG, see Chapter 1 FDA Documents) is sometimes problematic.

Consider also the possibility of providing a paper submission with an accompanying hyperlinked CD-ROM disk, allowing reviewers to move between electronic and paper versions. Some FDA groups may offer other suggestions as well.

6. **Schedule the submission.** Not only does the submission take some lead time planning (perhaps as much as six months for the development of an NDA—much less for other submissions), but there are other considerations as well.

An orphan-drug application and an IND both receive responses in about 30 days. Try to schedule submissions so that the response date will not fall within planned vacations or critical international travel. And both submissions (and many others) require an annual update report; it is best to stagger report due dates to avoid complications in the future.

But most important, to avoid submission bottlenecks, a clear schedule allows other team members—proofers, printers, collators, IT, QA, etc.—to make certain they are prepared. If QA needs a three-day period to review, count back a week (their three days, and two more to correct any problems they find) from the planned duplication, assembly, and submission dates.

7. **Designate contacts.** FDA submissions require a designated contact person, identified in the cover letter and (generally) in the submission itself. The contact person should be identified by name and title, with telephone (office and cell) and e-mail contact information provided.

But what if the contact person is ill, on vacation, traveling in Asia, or otherwise inaccessible? Rather than delay important FDA inquiries or information until the contact returns, most companies develop an alternate contact responsibility. The FDA wants a single name, but you can arrange to have other people monitor that person's e-mail account and telephone.

Some companies involved with a steady stream of multiple submissions establish a special e-mail address and telephone number

exclusively for FDA contacts. That box and number can be monitored by any company employee, who can then pass information on to the designated contact person.

Particularly in a time-critical environment, do not miss a message from FDA personnel. Because of their busy schedule, it may be several days before they try to make contact again.

8. **Keep the FDA informed.** Once a file has been opened through a meeting request, inquiry, or submission, the project is assigned to an FDA contact. That designated individual can serve as a conduit to appropriate directors, committees, review boards, and divisions.

Communication with the FDA contact can take a variety of forms; most will accept telephone calls and e-mails and will request formal, written communications when significant issues arise. But regardless of the format, keep your contact in the loop if schedules or plans change.

Remember, though, that all contacts—even contact reports of telephone conversations—will be appended to the file. Keep all questions clear and direct and avoid speculative questions. Use the contact to keep the FDA informed of all official issues, but nothing is “off the record.”

9. **Make appeal and legal action as very last possible steps.** Regulatory decisions on submissions are communicated to applicants through a variety of channels, including verbal (telephone calls), e-mails, and formal letters. With careful self-regulation through a thorough QA review prior to submission, you should gain some control over the process, avoiding many but not all unpleasant surprises.

If the review result is not what was anticipated or expected, there are several levels of response that are possible. The first, and generally most successful, is a conversation to pinpoint the problem, followed by a clarification (if the adverse result is due to a simple misunderstanding), submission amendment (if more detail or support is requested), or resubmission (if significant issues need to be addressed). These informal requests for reconsideration are often successful, particularly if approached in a cooperative framework.

The next steps are clearly confrontation in varying degrees of severity. For most divisions and groups to which a submission is directed, there is a formal appeals process (see Chapter 6). If not, or as a step beyond that appeals channel, the FDA Office of the Ombudsman has a dispute-resolution procedure. Finally, it is possible to bring suit against the FDA in Federal Court.

While these formal appeal processes are available, and while careful mechanisms are built into the procedures to avoid any spirit of retaliation, there is likely to be an adverse effect on the cooperative atmosphere that ought to prevail in FDA interactions. While it is certainly

appropriate to follow through on all available and appropriate avenues of appeal, these formal steps should be considered as the last possible steps, to be followed only when other informal and nonconfrontational procedures are exhausted.

10. **Build a partnership.** In an appropriately self-regulated environment, the working relationship between the FDA and a submitting organization should be one of cautious partnership, working together within a carefully designed legal and administrative framework to achieve common goals. Both parties share the same general objective: to bring proven safe and effective drug products to a public in need of the potential treatment, therapy, or preventive.

Not-for-profit organizations, including universities and research institutes, have a natural affinity for such partnership arrangements since they avoid the natural skepticism that comes from a profit motivation. But, even for profit, companies can create a virtual partnership by communicating clearly to the FDA—in action as well as words—a willingness to put public health and safety above short-term revenue goals.

In all FDA interactions—verbal, face-to-face, and in submissions—keep this principle of primary, genuine concern for public health and safety as an underlying theme. The result will be slow building of mutual trust into a true partnership. And, if concern for public health and safety is not your true primary purpose, you are in the wrong business.

SUMMARY

The submissions process can be traumatic. Whether you are a start-up company filing your first meeting request or a major pharmaceutical organization with an NDA for the latest blockbuster, there is a great deal resting on the process and the result.

A good portion of that trauma flows from a perception of loss of control: the submission is delivered and seems to enter a black box of FDA review with no clearly predictable outcome.

But that sense of control can be regained and the result made rational and predictable through a careful QA process that checks the submission against FDA established criteria and through the use of an internal, self-regulating review process that applies the checklist criteria used by the FDA to the submission development process.

For meeting requests, orphan-drug applications, INDs, NDAs, 505b(2) NDAs, Abbreviated New Drug Applications (ANDAs), Orphan Annual Reports, and Annual Reports, the tools, checklists, and FDA guidelines are provided. With this tool kit, your organization can regain control of a rational, predictable submissions process.

FDA GUIDELINES

Three general submission guidelines are provided:

Federal Regulations: This document provides a summary of (and links to) the relevant sections of the Federal Food, Drug, and Cosmetic Act, including 21 Code of Federal Regulations (CFR) part 210 (CMPs for Manufacturing; 21 CFR Part 211 (GMS for Finished Pharmaceuticals); and Guidance Documents for NDAs, ANDAs, and Out of Specification (OOS) Test Result Reporting.

FDA ESG: This document provides an overview of the process of electronic submissions and provides registration and confirmation processes as well as links to electronic submission requirements of the Center for Biologics Evaluation and Research (CBER), the Center for Drug Evaluation and Research (CDER), the Center for Veterinary Medicine (CVM), the Adverse Events Reporting System (AERS), and the Center for Devices and Radiological Health (CDRH).

Electronic Regulatory Submissions and Review (CDER): This document (from <http://www.fda.gov/cder/regulatory/ersr/default.htm>) provides specific ESG guidance for CDER submissions, including NDAs, INDs, and DMFs.

Federal Regulations

CFR. The final regulations published in the Federal Register (daily published record of proposed rules, final rules, meeting notices, etc.) are collected in the CFR. The CFR is divided into 50 titles, which represent broad areas subject to Federal regulations. The FDA's portion of the CFR interprets the Federal Food, Drug and Cosmetic Act and related statutes. Section 21 of the CFR contains most regulations pertaining to food and drugs. The regulations document the actions of drug sponsors that are required under Federal law.

- 21 CFR Part 210. Current Good Manufacturing Practice (CGMP) in Manufacturing Processing, Packing, or Holding of Drugs
- 21 CFR Part 211. CGMP for Finished Pharmaceuticals
- Federal Register Notices for Proposed Changes and Final Changes to CGMP. The Office of Compliance, Division of Manufacturing and Product Quality Web page provides links to in-process changes in CGMP regulations announced in the Federal Register.

Guidance Documents

Guidance documents represent the FDA's current thinking on a particular subject. These documents are prepared for FDA review staff and drug spon-

sors to provide guidelines for the processing, content, and evaluation of applications, and for the design, production, manufacturing, and testing of regulated products. They also provide consistency in the Agency's regulation, inspection, and enforcement procedures. Because guidances are not regulations or laws, they are not enforceable. An alternative approach may be used if it satisfies the requirements of the applicable statute, regulations, or both.

- Guideline on the Preparation of Investigational New Drug Products (Human and Animal) (Issued November 1992, posted March 2, 1998). This guidance provides practices and procedures for preparing investigational new drug products that comply with certain section of the CGMP regulations for finished pharmaceuticals (Title 21 of the CFR, Parts 210 and 211.)
- Draft Guidance for Industry: Investigating OOS Test Results for Pharmaceutical Production. September 30, 1998 This guidance provides the Agency's current thinking on how to evaluate suspect, or OOS test results. For purposes of this document, the term *OOS results* includes **all** suspect results that fall outside the specifications or acceptance criteria established in new drug applications.
- Draft Guidance for Industry: ANDAs: Blend Uniformity Analysis. This guidance provides recommendations on when and how blend uniformity analysis should be performed. The recommendations apply to original ANDAs and supplemental ANDAs for formulation and process changes. The Federal Register notice for this draft is also available.

CDER Manual of Policies and Procedures (MaPPs)

MaPPs are approved instructions for internal practices and procedures followed by CDER staff to help standardize the new drug review process and other activities. MaPPs define external activities as well. All MaPPs are available for the public to review to acquire a better understanding of office policies, definitions, staff responsibilities, and procedures.

- 4723.1 Standing Operating Procedures for NDA/ANDA Field Alert Reports. (Issued October 30, 1998, posted November 2, 1998). This MaPP establishes a system for evaluating NDA and ANDA Field Alert Reports and provides instructions to the responsible CDER units for handling those reports.

Compliance Policy Programs and Guidelines

- Compliance References. This Web site from the Office of Regulatory Affairs provides links to compliance policy guides, regulatory procedures

manuals, and other compliance-related information. Chapter 4 of the Compliance Policy Guide covers human drugs.

- Compliance Program Guidance Manual. These programs and instructions are for FDA field inspectors.
- Consistent Application of CGMP Determinations. The FDA cannot approve applications to market new drugs from companies that have been cited for CGMP violations. Similarly, disapproval of any drug marketing application based upon CGMP deficiencies must also lead to regulatory and/or administrative action against other products produced under the same conditions.

Compliance Questions and Answers

- Human Drug CGMP Notes. These memos are intended to enhance field/headquarters communications on CGMP issues in a timely manner. The document is a forum to hear and address CGMP questions, provide updates on CGMP projects, and clarify and help apply existing policy to day-to-day activities of FDA staff.

FDA ESG USER GUIDE

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Introduction

The business of the FDA is extremely information intensive. In recognition of this fact and of the potential benefits offered by information technology for assisting with the management of information, the FDA has undertaken a number of projects supporting the electronic submission of text and data from the industries it regulates.

One of these projects entails the establishment of an Agency-wide solution (referred to as the FDA ESG) for accepting electronic regulatory submissions. The FDA ESG enables the submission of regulatory information for review. The overall purpose of the FDA ESG is to provide a centralized, Agency-wide communications point for receiving electronic regulatory submissions, securely. The new Agency Gateway will enable the FDA to process regulatory information through automated mechanisms while it enables

- a single point of entry for the receipt and processing of all electronic submissions in a highly secure environment;
- automating current electronic processes such as the electronic acknowledgment of submissions; and
- supporting the electronic common technical document (eCTD).

The electronic submission process is defined as the receipt, acknowledgment, routing, and notification to a receiving center of the receipt of an electronic submission. In this definition,

- “receipt” means transfer of a submission from a sender’s system to a temporary storage area in the FDA ESG;
- “acknowledgment” to the sender means the submission was sent from the sender’s system and received by the Gateway;
- “routing” means delivering a submission to a center-level storage area and initiating a load process to place a submission into a center receiving system; and
- “notification” of a submission’s arrival is made to those individuals responsible for the Center’s receiving system.

Each of these terms denotes a step in the process of electronic submission delivery, and together, these steps comprise the whole scope of electronic submission delivery.

The FDA ESG is the central transmission point for sending information electronically to the FDA. Within that context, the FDA ESG is a conduit, or a “highway,” along which submissions travel to reach their final destination. It does not open or review submissions; it merely routes them to the proper destination.

The FDA ESG uses a software application certified to comply with secure messaging standards. The screen graphics provided in the FDA ESG Web Interface sections of this User Guide are from the application.

The objective of this User Guide is to provide industry participants with information and guidance on how to prepare and send documents through the FDA ESG. A list of submissions that the FDA ESG will accept is given in Table 1.2. This document provides a high level description of the electronic submission process via the FDA ESG.

Overview of the Registration Process

Registering to use the FDA ESG involves a set of sequential steps that are to be conducted for all submitters and types of submissions. The first steps in the process are designed to ensure that the FDA ESG can successfully receive electronic submissions and that the electronic submissions are prepared according to published guidelines. The testing phase is done using the FDA ESG test system. Once the sender has passed the testing phase, an account will be set up, allowing the submissions to be sent to the FDA ESG production system.

Figure 1.1 illustrates the steps in the process. The remaining subsections in this section will explain each of the steps in turn.

Apply for a Test Account. Organizations that wish to submit electronically to the FDA must apply for an account to establish themselves as Transaction Partners. The term “Transaction Partner” refers to

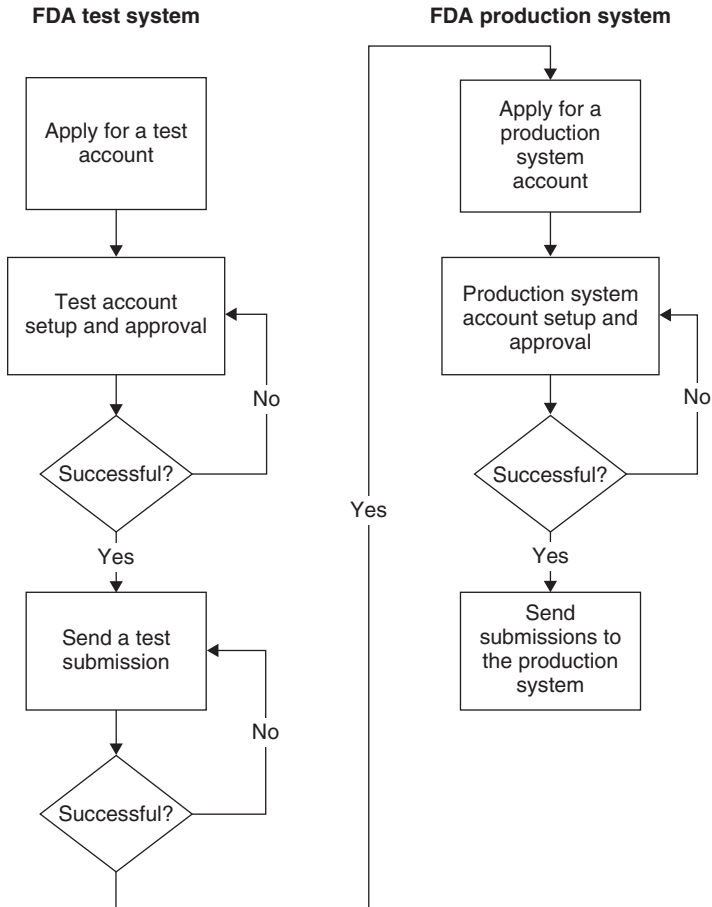


Figure 1.1 Overview of the registration process

an external entity authorized by the FDA to submit electronic submissions. Authorization includes agreement to regulatory conditions, successful completion of a certification process, and FDA administrative inclusion as a Transaction Partner.

Application for a test account must be initially requested for the FDA ESG. This is done to enable Transaction Partners to send a test submission to the FDA ESG.

Applying for an account involves information-sharing activities between the Transaction Partner and the FDA to set up transmission, receipt, and identification parameters. This ensures the correct identification of the Transaction Partner to the FDA. Digital certificate information is provided to the FDA as part of the application.

Test Account Setup and Approval. The account application is reviewed by the FDA ESG Administrator. The Administrator verifies that a letter of nonrepudiation agreement is on file, that the digital certificate conforms to the X.509 version 3 standard, and that all data fields in the **Issuer** and **Subject** fields are completed (see *Appendix A, Digital Certificates* for more information). The Administrator will also communicate with the Transaction Partner to confirm the application information. If these conditions are met, a test account is set up, and connections to the FDA ESG test system are established before the submitting organization is approved as a Transaction Partner.

Send a Test Submission. By sending a test submission, the Transaction Partner ensures the following conditions are met.

- The test submission is received by the FDA ESG. A notification is sent by the FDA ESG, confirming that the submission was successfully received.
- The submission is routed to the correct Center Holding Area.
- The submission is prepared according to regulatory guidelines. The Center sends an acknowledgment confirming that the submission was prepared correctly.

During the testing process, Transaction Partners who will be sending submissions larger than 1 GB will be asked to send a 7.5-GB test submission. This test will allow Transaction Partners to identify and resolve network limitations that will impact the speed of delivery. Send 7.5-GB test submissions to the GW TEST Center and select “SIZE TEST” as the submission type.

When testing connectivity, do not send the submission to the actual Center. Instead, send all connectivity test submissions to the GW TEST Center with the submission type “CONNECTION TEST.” Only guidance compliance test submissions should be sent to the FDA Center.

Apply for a Production System Account. Applying for a Production System Account in the FDA ESG follows the same process as applying for a test account. (see “Apply for a Test Account”)

Production System Account Setup and Approval. The same process is followed to setup a Production System Account as for a Test Account (see “Test Account Setup and Approval”).

Send Submissions to the Production System. After completion of these steps, the Transaction Partner is enabled and approved to send submissions to the FDA ESG. The Production System Account allows the Transaction Partner to send any of the supported submission types to the FDA. **However, the FDA**

will process those submission types only for which the Transaction Partner has received prior approval.

NOTE: It is the responsibility of the Transaction Partner to consult the appropriate FDA Center for information on formats, deadlines, and other information or procedures for submissions.

Preparatory Activities

There are a number of preparatory activities that need to be completed before beginning the registration process. This section describes these preparatory activities and presents system and protocol issues for FDA ESG users to consider.

Submit Letter of Nonrepudiation Agreement. A letter of nonrepudiation agreement **must** be submitted to the FDA. See *Appendix B, Sample Letters of Nonrepudiation Agreement*, for letter examples.

The nonrepudiation agreement allows the FDA to receive electronically signed submissions in compliance with 21CFR Part 11.100.

Obtain Digital Certificate. A digital certificate must be obtained.

Digital certificates ensure private and secure submission of electronic documents. The digital certificate binds together the owner's name and a pair of electronic keys (a public key and a private key) that can be used to encrypt and sign documents.

Digital certificates can be obtained from either a public or a private Certificate Authority. It must be an X.509 version 3 certificate, and all data fields in the **Issuer** and **Subject** fields must be completed. See *Appendix A, Digital Certificates* for more information on digital certificates.

Understand Submission Guidelines. Each FDA Center has specific guidelines that must be followed for successful submission. Table 1.1 contains links to Center-specific preparation guidelines and contacts. Table 1.2 lists electronic submissions supported by the FDA ESG. Important information on the use of digital/electronic signatures on FDA forms can be found in *Appendix C, Digital Signatures*.

The submission acronyms or names listed in Table 1.2 are not to be used as attributes in the submission header. See Table G-1 in *Appendix D, AS2 Header Attributes*, for a list of allowed attributes for the different submission types.

Naming Conventions. A special consideration applies to the naming convention for files and directories. The following characters are not recommended for use when naming submission files and directories.

/—forward slash

\—backslash

TABLE 1.1 FDA links to submission preparation guidelines

Center	Link
Center for Biologics Evaluation and Research (CBER)	http://www.fda.gov/cber/esub/esub.htm
Center for Drug Evaluation and Research (CDER)	http://www.fda.gov/cder/regulatory/ersr/default.htm
Center for Devices and Radiological Health (CDRH)	http://www.fda.gov/cdrh/cesub.html
Adverse Event Reporting System (AERS)	http://www.fda.gov/cder/aerssub/default.htm
Center for Veterinary Medicine (CVM)	http://www.fda.gov/cvm/esubstoc.html

Note: Meeting the requirements for using the FDA ESG to route submissions does not mean that these submissions automatically meet FDA Center-specific submission requirements.

For each test submission type, a test submission must be validated by the Center before sending submissions to the Production System.

It is the responsibility of the Transaction Partner to consult the appropriate FDA Center for information on formats, deadlines, and other information or procedures for submissions.

TABLE 1.2 Electronic submissions supported by the FDAESG

Center	Submissions
CBER	AERS—Adverse Event Reports
	AERS—Attachments
	BLA—Biologics License Application (eCTD and eBLA format)
	eCTD—Electronic Common Technical Document
	IDE—Investigational Device Exemption
	IND—Investigational New Drug Application (eCTD and eIND format)
	DMF—Drug Master File
CDER	Promotional Materials
	Lot Distribution Data
	AERS—Adverse Event Reports
	AERS Attachments
CDRH	ANDA—Abbreviated New Drug Application
	BLA—Biologics License Application (eCTD and eBLA format)
	eCTD—Electronic Common Technical Document
	NDA—New Drug Application (eCTD and eNDA format)
	IND—Investigational New Drug Application
CVM	Adverse Events
	Electronic Submissions
GW TEST ^a	Electronic Submissions
	CONNECTION TEST
	SIZE TEST

^aThese submission types are supported in the test environment only and are intended solely for testing.

:—colon

?—question mark

“—quotation marks

<—less than sign

>—greater than sign

|—vertical bar,

space—If you need to use a space, use `_an_underscore_instead` or `SeparateWordsWithCapitalLetters`.

Note: Directories and subdirectories cannot begin with the “.” (dot) character.

Determine Submission Method. There are three options for sending FDA ESG submissions.

1. FDA ESG Web Interface sends submissions via Hyper Text Transfer Protocol Secure (HTTPS) through a web browser according to Applicability Statement 2 (AS2) standards.
2. Applicability Statement 1 (AS1) Gateway-to-Gateway is an electronic submission protocol that uses secure e-mail for communications.
3. Applicability Statement 2 (AS2) Gateway-to-Gateway is an electronic submission protocol that uses HTTP/HTTPS for communications.

Determining the best of these options for your organization will be influenced by the types of submissions to be transmitted, infrastructure capabilities, and business requirements.

One or more of these options can be selected to submit electronic documents to the FDA. However, a separate registration will be required for each option selected.

Considerations for each option are shown in Table 1.3.

A factor that determines how quickly a submission can be sent to the FDA ESG is the Transaction Partner’s network connection to the Internet. Table 1.4 lists the maximum transmission rates for a variety of network connections and the optimal time it would take to send a 1-GB submission.

Actual times will be greater than those listed in the table due to factors such as network configuration and the amount of traffic coming in and going out through the line. For example, submissions sent in the middle of the day typically take 1.5–2 times longer to send than those sent after business hours. Pilot testing with selected Industry Transaction Partners has shown that it takes approximately 24h for submissions 15GB to 25GB in total size to be transmitted and processed by the FDA ESG. These companies had T3 network connections or better. FDA recommends that submissions of this size be sent overnight, starting at 4:30 p.m. EST, for the submission to be received by the target Center before the end of the next business day.

TABLE 1.3 Considerations for submission protocol choice

Transaction partner considerations	FDA ESG Web Interface	AS1 Gateway-to-Gateway	AS2 Gateway-to-Gateway
Cost	None	High setup and support costs	High setup and support costs
Setup	Minimal	Need to install and configure Gateway	Need to install and configure Gateway
User-friendly Web interface	Yes	No	No
Submission types supported	All, including AERS reports	AERS Reports and AERS Attachments only	All, including AERS reports
Long-term support by FDA	Yes	This particular protocol will be phased out in May 2007	Yes
Preparation of multfile submissions ^a	Occurs automatically	Not applicable	Multifile submissions need to be archived and compressed by using a tar and gzip utility prior to submission
Custom attributes for submission routing ^b	Automatically adds custom attributes to the AS2 header	Not applicable	Need to add custom attributes to the AS2 header
Integration to back-end systems	No	Can be automated	Can be automated
Tracking of submission activity by Transaction Partner	Manual tracking	Can be automated	Can be automated
Automation of submission process	No	Yes	Yes

^aSee Appendix E, *Creating tar Files and Compressing Files for Submission*.

^bSee Appendix D, *AS2 Header Attributes*.

During the testing process, Transaction Partners who will be sending submissions larger than 1GB in total size will be asked to send a 7.5-GB test submission. This test will allow Transaction Partners to identify and resolve network limitations that will impact the speed of delivery.

TABLE 1.4 Transmission rates for network connections and optimal times for transmission

Network connection	Max. transmission rate (Mbps)	Time (min)
		1 GB
T1	1.54	83
T2	6.31	21
T3	44.7	3
OC1	51.8	2.5
OC3	155.4	0.8
T4	274.8	0.5
OC12	621.6	0.2

Mbps = Megabits per second.

1 GB (Gigabyte) = 8,590 Megabits.

Connection Requirements. FDA ESG Web Interface users need the following:

- A high-speed Internet connection
- A web browser, either Internet Explorer 6 (or later) or Mozilla Firefox 1.0 (or later)
- Hard disk space of at least three times the size of the submission. For instance, if the submission is 1 MB in size, then at least 3 MB of hard disk space is required.
- Sun’s Java Runtime Edition (JRE) 1.5.10, for the browser plug-in files

See *Appendix F, Java Runtime Edition Installation* for more information on obtaining and installing JRE.

Gateway functionality is optimized with JRE version 1.5.10 installed. It is recommended that the automatic Java update option on the computer be disabled to avoid the automatic installation of a different version of JRE. The steps to do this are as follows:

1. Select Control Panel from the Start menu.
2. Double-click on the Java (or Java Plug-In) icon.
3. Click on the “Update” tab.
4. Uncheck the “Check for Updates Automatically” checkbox.
5. Click OK.

Gateway-to-Gateway users need the following:

- A high-speed Internet connection
- An AS1- and AS2-compliant Gateway product
- Hard disk space of at least three times the size of the submission

TABLE 1.5 Submission process aspects and help and information contacts

Submission process aspect	Contact
Preparation/Registration/Policy Questions	e-mail: esgprep@fda.gov
Technical Issues with Submissions after becoming a Production System Transaction Partner	FURLS Help Desk: 1-800-216-7331, available from 7:30 a.m. to 11:00 p.m., EST www.cfsan.fda.gov/~furls/helpf2.html (This Web site also contains an e-mail link.)
Center-specific Submission Guidance	See “Understand Submission Guidelines.”

NOTE: AERS submissions can be sent by using the AS1 protocol. All other types of submissions, including AERS, can be sent by using the AS2 protocol.

Help and Information. There are resources that can be contacted if you need assistance with various aspects of the submission process. These are provided in Table 1.5.

FDA ESG Web Interface Electronic Submissions

The steps for the electronic submission process for FDA ESG Web Interface users are provided in the following sections.

Apply for a Test Account. Applying for an FDA ESG Web Interface Test account is a multistep process. Before beginning the process, the following information should be known:

- Company and contact information
- Digital certificate file location

The FDA ESG Web Interface address and a temporary Login ID and password can be obtained from the FDA ESG Administrator by sending an e-mail to esgprep@fda.gov indicating intent to register for the FDA ESG.

The remainder of this section describes the FDA ESG Test Account Application process using screen shots from the FDA ESG Web Interface.

1. Using the address provided by the FDA, access the FDA ESG Web Interface.

The **Login** page is displayed. Note the test environment warning on the **Login** page. If the **Login** page does not have this warning, do not continue. Exit the browser and contact the FDA ESG Administrator at esgprep@fda.gov to request access to the test environment.



- 2. Enter the **User ID** and **Password** that was provided by the FDA and click the **Login** button.

The **Welcome to the WebTrader registration wizard** page is displayed. This wizard guides the Transaction Partner through the remainder of the application process.

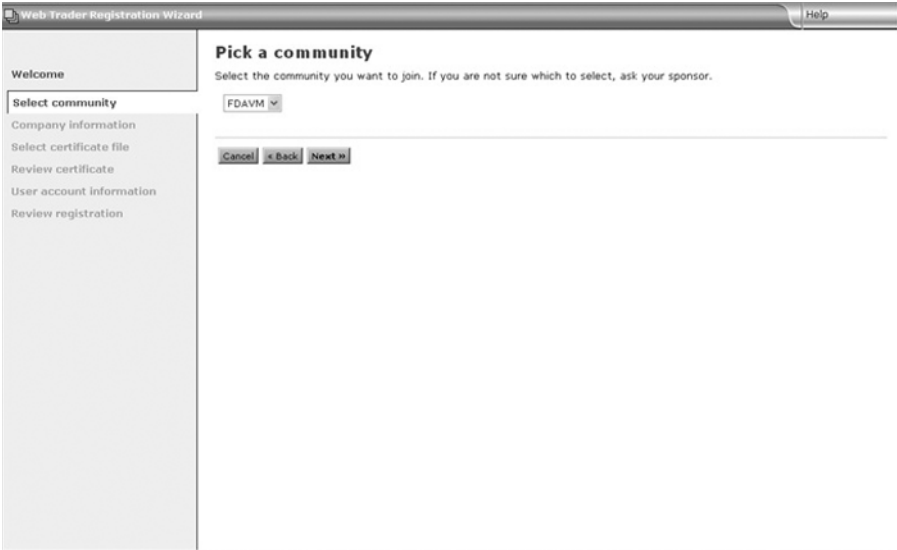


3. Click the **Next** button.

The **Pick a community** page is displayed

The community represents where submissions will be sent for logging, verification, and ultimately routing to the appropriate FDA Center. The only community will be “FDA VM.”

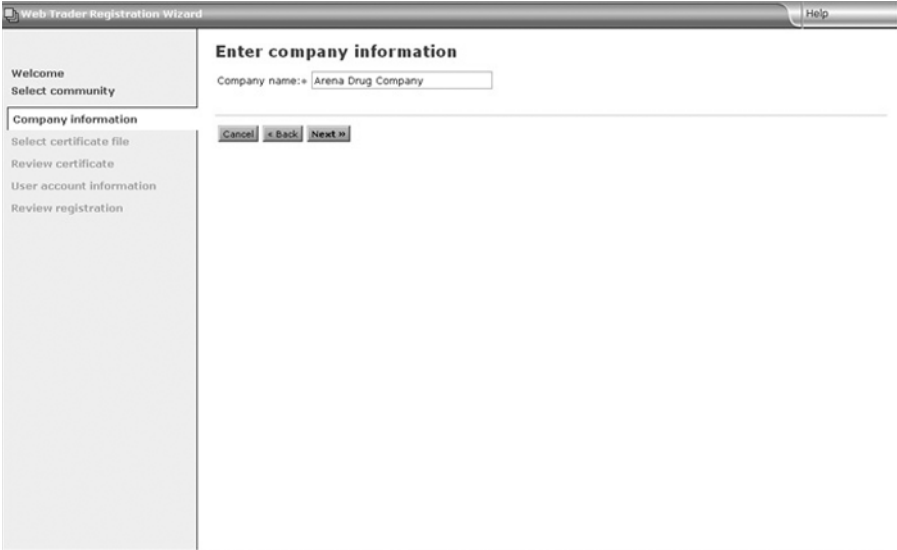
See *Appendix G, Glossary of Terms*, for more information about the community.



4. Click the **Next** button.

The **Enter company information** page is displayed.

This page records your company’s name for identification purposes.



NOTE: Partners who have an existing account, whether it is AS1, AS2, or WebTrader, must enter a unique string (different from the one used when registering for their first account) in the “Company name” field. This is to ensure that this account is treated as a separate identity in the database.

5. Click the **Next** button.

The **Locate the certificate file** page is displayed.

This page is used to specify the location of the certificate file. Each submission must be accompanied by a certificate. The digital certificate must be an X.509 version 3 certificate.

See *Appendix A, Digital Certificates* for more information about digital certificates.

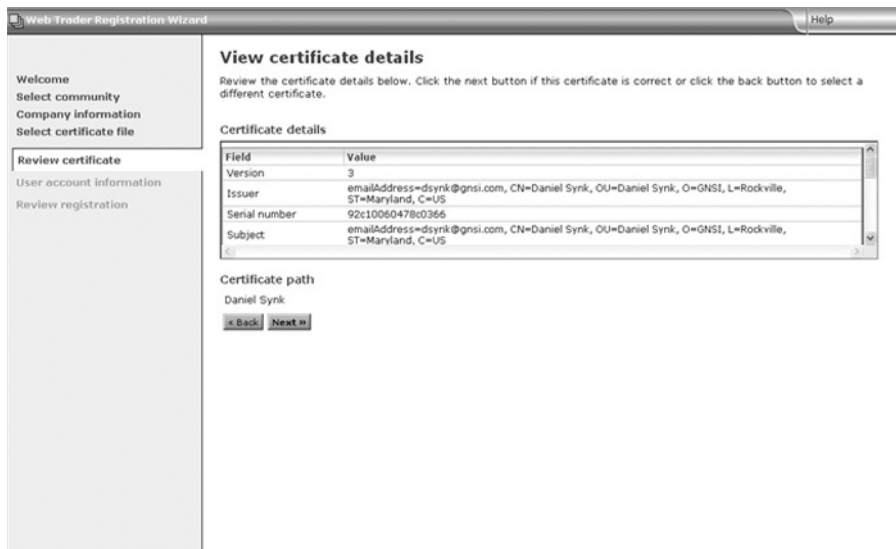
The screenshot shows a web browser window titled "Web Trader Registration Wizard" with a "Help" button in the top right corner. On the left is a vertical navigation pane with the following menu items: "Welcome", "Select community", "Company information", "Select certificate file" (which is highlighted), "Review certificate", "User account information", and "Review registration". The main content area is titled "Locate the certificate file" and contains the instruction: "Enter the name of the certificate file to import. The file must have an extension of .cer, .p7b, or .p7c." Below this is a text input field containing the path "C:\Documents and Settings\dsynk\Desktop\DanielSynk.p7b" and a "Browse..." button. At the bottom of the main area are three buttons: "Cancel", "< Back", and "Next >".

NOTE: There are situations where a valid certificate is not accepted by the registration module and an error message is returned. If this occurs, zip the certificate file and e-mail it to FDA ESG Administrator at esgprep@fda.gov. Once received, the FDA will assess the certificate and send a response.

6. Provide the desired digital certificate file in the **Certificate file** field by entering the name of the certificate or browsing for one on your hard drive by clicking on the **Browse ...** button.

The **View certificate details** page is displayed.

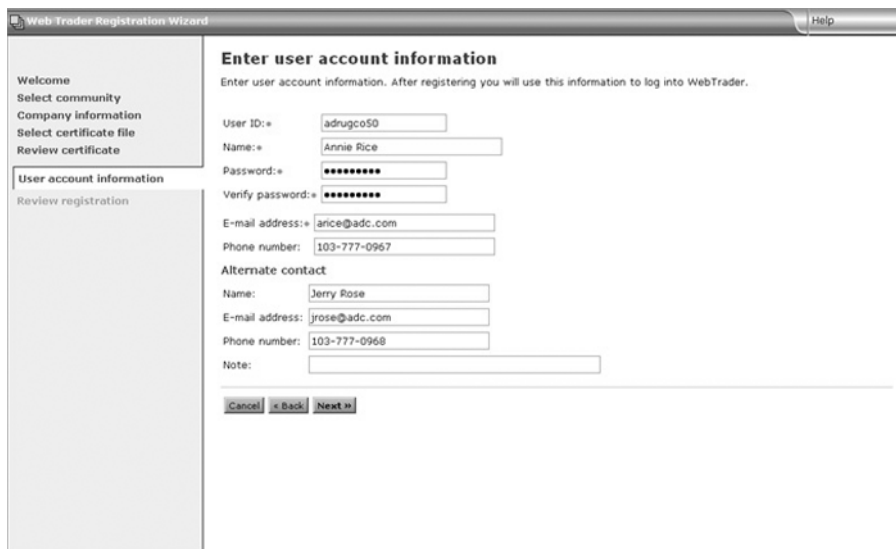
This page is used to review the certificate information and to assign a name to the certificate. Carefully review the **Issuer** and **Subject** fields to be sure that all data fields are completed (i.e., for each data element such as “CN,” there is a value that follows the equal sign).



7. Click **Next**.

The **Enter user account information** page is displayed.

This page is used to specify the user ID, password, and contact information selected by the Transaction Partner. After registration is complete, this user ID and password will be used by the Transaction Partner to log on to the FDA ESG Web Interface.



8. Enter a new login user ID and password. Remember this user ID and password—it will be used for subsequent logins.
9. Click **Next**.

The **Registration summary** page is displayed.
This final page provides an account summary.

Web Trader Registration Wizard Help

Welcome

- Select community
- Company information
- Select certificate file
- Review certificate
- User account information

Review registration

Registration summary

Review the information below. Click the finish button to submit this registration or click the back button to make changes.

Once you submit this registration, you can use your user ID and password to log on immediately to WebTrader, but you will not be able to successfully send documents until the sponsor authorizes your registration.

Company information

Company name: Arena Drug Company
Sponsor: FDAVM
Certificate: emailAddress=dsynk@gnsi.com, CN=Daniel Synk, OU=Daniel Synk, O=GNSI, L=Rockville, ST=Maryland, C=US

User account information

User ID: adrugco50
Name: Annie Rice
Phone number: 103-777-0967
E-mail address: arice@adc.com

Alternate contact

Contact name: Jerry Rose
Phone number: 103-777-0968
E-mail address: jrose@adc.com
label.commet:

I hereby certify that the information provided herein is true and that I am authorized to register with the FDA.

Cancel < Back **Finish**

10. Check the box to certify the accuracy of your information.
11. Click the **Finish** button to return to the **Login** page, or close the browser window.

Test Account Setup and Approval. After a successful Test Account setup, the FDA sends an e-mail to the e-mail address provided for the contact, indicating approval as a Transaction Partner and authorization to send a test submission. Typically, the approval notification is sent on the next business day.

The test submission cannot be sent until this notification has been received.

JRE must be installed to send a submission. See *Appendix F, Java Runtime Edition Installation* for the installation procedures.

Once you have fulfilled these criteria, proceed to the next section for instructions on sending a test submission.

Send a Test Submission. After Test Account Setup and Transaction Partner approval, a test submission must be sent to ensure that the submission “conduit” is working properly from end to end. To do this, follow the steps below.

Confirm that the correct version of the JRE is installed before you begin. See *Appendix F, Java Runtime Edition Installation* for the version information and installation procedures.

1. Using the address provided by the FDA, access the FDA ESG Web Interface application.

The **Login** page is displayed.

FDA U.S. Food and Drug Administration Department of Health and Human Services

FDA Electronic Submissions Gateway

User ID:

Password:

I agree to the terms set forth in the System Notification below.

Remember my user ID

Pop-up blocking software for your browser may interfere with this product. You may want to disable or uninstall such software.

YOU ARE ENTERING THE FDA ELECTRONIC SUBMISSIONS GATEWAY TEST ENVIRONMENT. THIS ENVIRONMENT IS TO BE USED FOR TEST SUBMISSIONS ONLY.

System Notification: This computer system, including all related equipment, networks and network devices (specifically including Internet access), is provided for authorized U.S. Government use. This computer system may be monitored for all lawful purposes, including ensuring that its use is authorized, for management of the system, to facilitate protection against unauthorized access, and to verify security procedures, survivability and operational security. Use of this computer system, authorized or unauthorized, constitutes consent to monitoring of this system. Unauthorized use may subject you to criminal prosecution, and/or administrative disciplinary action including having access privileges revoked. Under 18 U.S.C. 1001, anyone who makes a materially false, fictitious, or fraudulent statement to the U.S. Government is subject to criminal penalties.

Licensed to: [FDA](#)

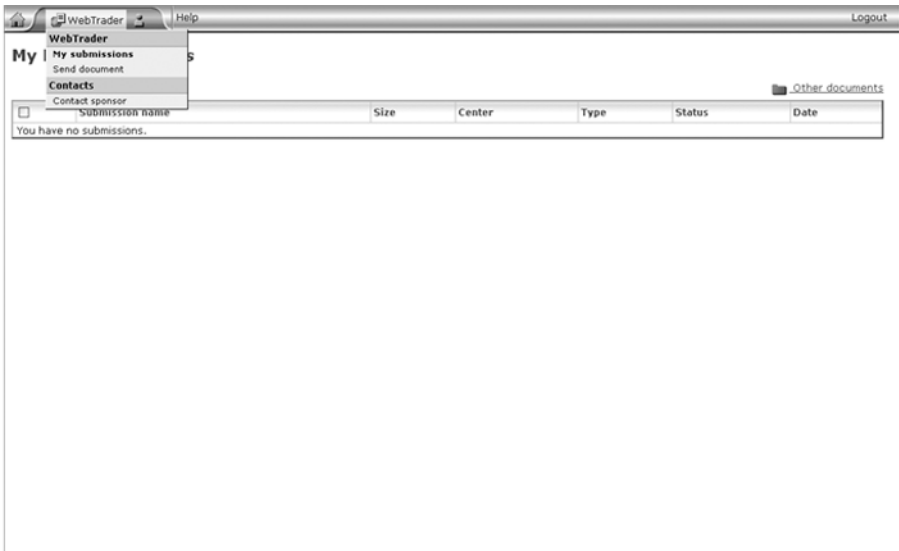
Note the test environment warning on the **Login** page. If the **Login** page does not have this warning, do not send a test submission. Exit the browser and contact the FDA ESG Administrator at esgprep@fda.gov to request access to the test environment.

2. Enter the **user ID** and **password** that were set up in the registration wizard (see “Apply for a Test Account”).
3. Click the **Login** button.

After a successful login, the **My FDA submissions** page is displayed. This page lists all messages received from the FDA ESG.



- 4. Click the **WebTrader** icon.
The **WebTrader** drop-down menu is displayed.



5. Select the **Send document** menu item.
The **Send document** page is displayed.

Send document

Select who will receive the document

Gateway: FDAVM

Center:

Select the contents of the submission

Enter a path to a file or a directory. If a directory is entered, then the entire contents of the directory will be included in the submission. All the paths stored in the submission will be relative from the provided directory path unless an alternate root directory is entered.

Path:

Root directory:

Submission type:

Select a signing certificate

Current file: No certificate selected

New file:

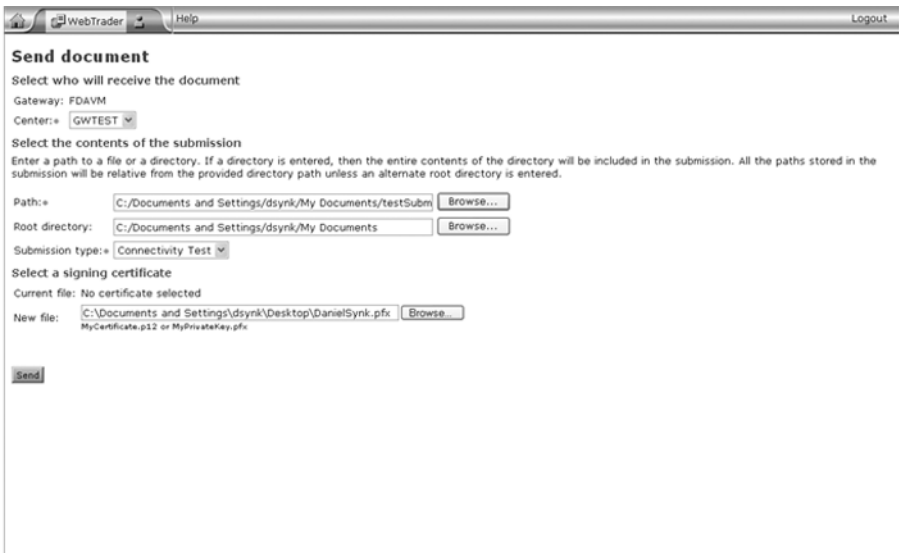
MyCertificate.p12 or MyPrivateKey.pfx

6. Select an FDA Center from the **Center** drop-down box. The Centers that can be selected at present are CBER, CDER, CDRH, CFSAN, CVM, or TESTING. Upon choosing a Center, the **Submission type** drop-down box will be populated with the correct submission types for that Center.
 7. For single-file submissions, click the **Browse** button associated with the **Path** text box to select the test submission.
 8. For multifile submissions, click the **Browse** button associated with the **Root Directory** text box to select the directory that contains all the files in the test submission. Make sure that the name of any file or subdirectory does not start with “.” (dot). **Note:** The **Path** field is still required for multifile submissions. Make sure you have entered a path as well as a root directory.
 9. Select a test submission type from the **Submission type** drop-down box.
- About submission types:**
- **Connectivity tests** ensure that your connection to the ESG is up and running. They should be sent to the “Testing” Center.
 - **Load tests** ensure that you are able to send large submissions through the ESG; you should perform a load test if you are planning on sending submissions larger than 100MB. Load tests should be sent to the “Testing” Center. See “Sending Large (>7.5 GB) Submissions” section.

- **Guidance-compliant submission tests** are reviewed by your Center so it can clear you for a production account. Guidance-compliant submissions should be sent to your Center.
10. Select a signing certificate by clicking the associated **Browse** button and selecting the signing certificate. All submissions require a certificate to digitally sign and encrypt the submission.

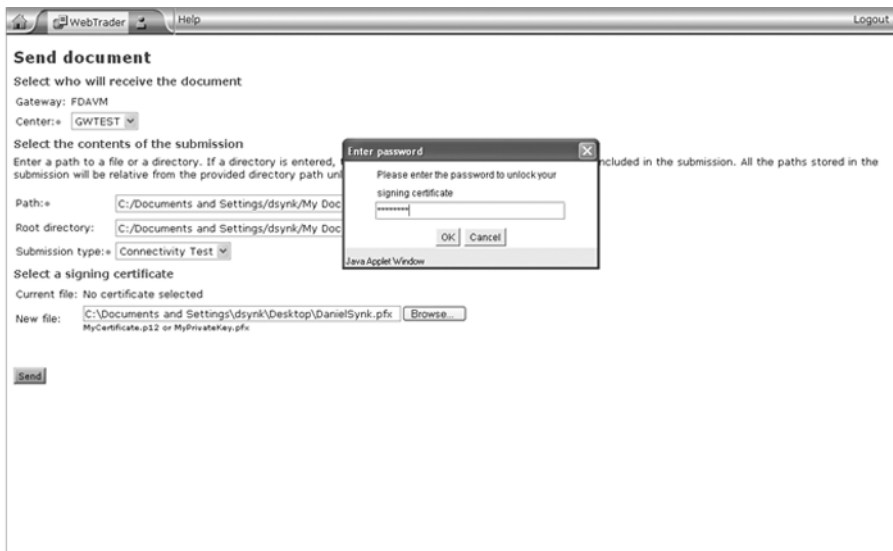
Note that connectivity tests should only be sent to TESTING, not actual centers.

The completed **Send document** page should be populated similar to the page below.

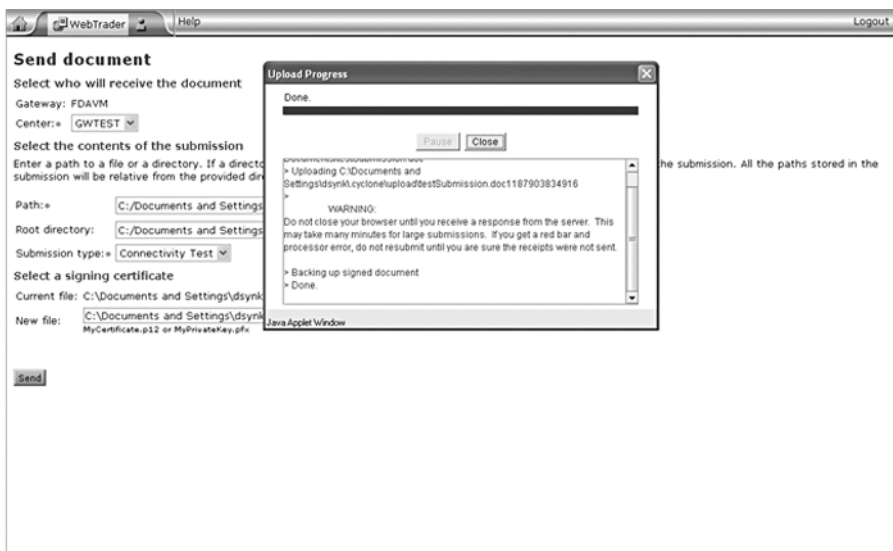


11. Click the **Send** button on the **Send document** page.

The **Enter password** dialog box is displayed on top of the **Send document** page.



12. Enter the certificate password and click **OK** in this dialog box. The **Upload Progress** dialog box is displayed on the **Send document** page:



13. When the upload is complete (indicated by the display of **Done**), click the **Close** button in the **Upload Progress** dialog box. At this point, the test submission is sent. The FDA ESG logs the submission and verifies submission destination and type. When the

submission is successfully received at the FDA, a receipt e-mail will be listed on the **My FDA Submissions** page.

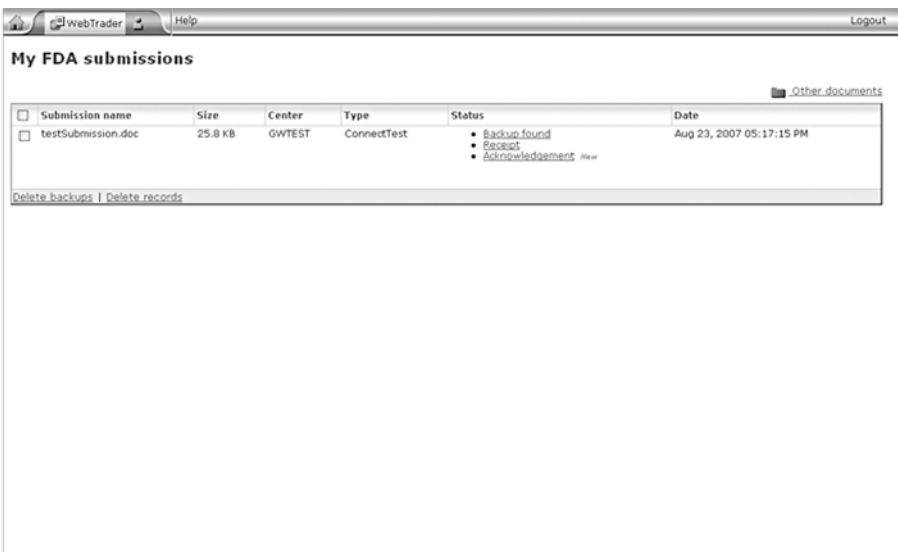
14. To access the receipt, click on the **WebTrader** icon to access the Inbox.

The **WebTrader** drop-down menu is displayed.



15. Select the **My Submissions** menu item.

The **My FDA submissions** page is displayed.



The receipt for the test submission should be displayed here. This first receipt confirms that the submission was received by the FDA ESG. Click on the **Details** link to access the receipt contents.

If there are any errors in the submission, the receipt will not appear on the **My FDA submissions** page but will be sent to the Documents in the Inbox page. The receipt will contain information about why the submission failed.

The FDA ESG will then route the test submission to the Center Holding Area. When the Center system successfully receives the submission, a second acknowledgment will be sent confirming that the Center has received the submission. The Center will then validate the test submission.

Contact the FDA ESG testing representative at esgprep@fda.gov if the receipt for the test submission or the Center acknowledgement is not received.

The next step is to apply for an FDA ESG Production System Account. This process is described in the following section.

Sending Large (>7.5 GB) Submissions The FDA ESG is able to receive and process regulatory submissions up to 100 GB. The major consideration in determining how quickly large submissions are transmitted to the FDA ESG is the bandwidth available to the Transaction Partner between their company and the FDA ESG. The FDA has the following recommendations concerning the transmission of large regulatory submissions.

- During the testing phase, send a 7.5-GB test submission. This test will allow Transaction Partners to evaluate bandwidth availability and to adjust their network configuration as necessary. This test submission should be sent to the “Testing” Center with “7.5 GB Submission” as the submission type.
- Send a 7.5 GB test submission that is representative of an actual submission. The Web Interface archives and compresses the submission into a single file prior to transmission. Submissions that consist of text files will compress to a greater extent than portable document format (PDF) files, will transmit faster, and thus give an inaccurate assessment of the time it takes for submissions to be sent and processed by the FDA ESG.
- Send submissions greater than 7.5 GB overnight. Pilot testing with selected Industry Transaction Partners has shown that it takes approximately 24 h for submissions 15–25 GB in total size to be transmitted and processed by the FDA ESG. These companies had T3 network connections or better. FDA recommends that large submissions be sent overnight, starting at 4:30 p.m. EST, for the submission to be received by the target Center before the end of the next business day.

Sending large submissions may result in the FDA ESG Web interface erroneously reporting that the transmission was not successful, even though the

FDA ESG has successfully received the transmission. This is a known bug, and the FDA has asked Axway to provide an update to the Web interface that fixes this error.

When the FDA ESG has received a complete submission, a backup copy is made before the Java applet receives a reply from the server confirming the submission is complete. For large submissions (>7.5 GB), this can take many minutes. Since there is no network activity for such a long time, the session has time-outs and the Java applet never receives the response. The FDA ESG has received the submission successfully, but the Java applet returns an error and indicates that the submission needs to be resumed. Receipt of the first acknowledgment [Message Delivery Notification (MDN)] confirms that the submission was successfully received by the FDA ESG and that it is okay to cancel the resume request. Since this is a large submission, it will take several hours before the first acknowledgment is received.

If you receive this error and it has clearly occurred at the end of the transmission, do not resend the submission right away. Wait for several hours (or longer, depending on the size of the submissions) and see if the MDN is sent before attempting to resend the submission.

Apply for a Production System Account. The steps for applying for an FDA ESG Production System Account are the same as those described in “Apply for a Test Account” section.

However, there is a difference in the **Login** page. The **Login** page *should not* have the test environment warning that it has when sending a test submission; it should look like the **Login** page shown below:



FDA U.S. Food and Drug Administration Department of Health and Human Services

FDA Electronic Submissions Gateway

User ID

Password

Remember my user ID

Login

Licensed to: FDA

Pop-up blocking software for your browser may interfere with this product. You may want to disable or uninstall such software.

If the **Login** page does have the warning, do not send a submission. Exit the browser, contact the FDA ESG Administrator at esgprep@fda.gov, and obtain the correct address for the FDA ESG **Login** page.

Production System Account Setup and Approval. After successful completion of the Production System Account setup, the FDA sends an e-mail to the e-mail address provided for the primary contact, indicating approval as a Transaction Partner and authorization to send submissions to the FDA ESG. Typically, the approval notification is sent on the next business day.

Submissions cannot be sent to the FDA ESG until this notification has been received.

Send Submissions to the Production System. The steps to send a Submission to the FDA ESG are the same as those in the “Send a Test Submission” section.

However, there is a difference in the **Login** page. The **Login** page *should not* have the test environment warning that it has when sending a test submission; it should look like the **Login** page shown in the “Apply for a Production System Account” section.

If the **Login** page does have the warning, do not send a submission. Exit the browser, contact the FDA ESG Administrator at esgprep@fda.gov, and obtain the correct address for the FDA ESG **Login** page.

Tracking Submissions. Once a submission has been sent by using the FDA ESG Web Interface, the Transaction Partner can track the submission to ensure that it was received by the FDA ESG and the Center.

The Submission Process When a submission is sent by using the FDA ESG Web Interface, it goes through the following steps.

1. The submission is transmitted by using the FDA ESG Web Interface to the Gateway. When the FDA ESG receives this submission, it sends a receipt known as an MDN to the Inbox of the account from which the submission was received.
2. The submission is delivered from the FDA ESG to a central holding area for all the Centers.
3. The submission is then delivered from the holding area to the appropriate Center. When a Center receives a submission, it sends an acknowledgment to the Inbox of the account from which the submission was sent.

MDNs and Acknowledgments When a submission is sent by using the FDA ESG Web Interface, the following two messages are delivered to the Inbox of the account from which the submission was sent.

1. A receipt from the FDA ESG, also known as an MDN. This message denotes that the submission has been delivered to the FDA ESG. The name of the receipt message includes the file name of the submission that was sent. If a directory of files was submitted, the file name of the submission will be the name of the directory followed by the extension “.tar.gz”. The MDN message contains the message ID of the submission and a date stamp for when the submission was received by the FDA ESG. These items may be used to track a submission.
2. An acknowledgment from the Center to which the submission was sent. This file is named with a unique alphanumeric string known as the Core ID. The Core ID is also used by the FDA ESG to track a submission.

A sample Inbox looks similar to this, once submissions have been sent:

My FDA submissions  [Other documents](#)

<input type="checkbox"/>	Submission name	Size	Center	Type	Status	Date
<input type="checkbox"/>	testSubmission.doc	25.8 KB	GWTEST	ConnectTest	<ul style="list-style-type: none"> • Backup found • Secure • Acknowledgment <small>view</small> 	Aug 23, 2007 05:17:15 PM

[Delete backups](#) | [Delete records](#)

Message IDs and Core IDs Among other information, the MDN contains a Message ID and a time stamp denoting the time the submission was received. The Message ID is a unique alphanumeric string that identifies each submission. This Message ID can also be used to track a submission and to correlate a submission to its Center acknowledgment.

A sample MDN looks similar to the file shown below. The Message ID and date stamp in this MDN are highlighted.

```

Message-ID: <1140124426654.2852@llnap01>
Date: Thu, 16 Feb 2006 21:13:46 GMT
From: esgprep@fda.gov
Subject: AcmeDrugCompany; ZZFDA
Mime-Version: 1.0
Content-Type: multipart/signed; micalg=sha1; protocol="application/pkcs7-
signature"; boundary="-----_Part_65_16583928.1140124426654"
X-Cyclone-From: ZZFDA
X-Cyclone-To: AcmeDrugCompany
Content-Length: 1952

-----=_Part_65_16583928.1140124426654
Content-Type: multipart/report; report-type=disposition-notification;
boundary="-----_Part_64_17446017.1140124426654"

-----=_Part_64_17446017.1140124426654
Content-Type: text/plain; charset=us-ascii

This MDN (Message Disposition Notification) was automatically built on
Thu, 16 Feb 2006 21:13:46 GMT in response to a message with id
<12689343.1140124473009.JavaMail.sacharya@pvenkat> received from
ZZFDA on Thu, 16 Feb 2006 21:13:46 GMT.
Unless stated otherwise, the message to which this MDN applies
was successfully processed.

-----=_Part_64_17446017.1140124426654
Content-Type: message/disposition-notification

Original-Message-ID: <12689343.1140124473009.JavaMail.sacharya@pvenkat>
Disposition: automatic-action/MDN-sent-automatically; processed
Received-Content-MIC: Jkm19bjOa6J8JBn/pv87oYIBnTA=, sha1

```

When a Center receives a submission, it associates the submission's Message ID with a Core ID. This Core ID can be used along with the Message ID generated as part of the MDN to track a submission on the FDA ESG. A sample acknowledgment message with the Core ID highlighted is shown below:

```

MessageId: <12689343.1140124473009.JavaMail.sacharya@pvenkat>

CoreId: 1140124426155.2844@llnap01

DateTime Receipt Generated: 02-16-2006, 16:17:11

The date and time stamp contained in this message conveys when CBER
received your submission from the Electronic Submission Gateway. If
your submission was received at CBER after 4:30 PM EST, the official
receipt date for the submission is the next government business day.

```

Accessing MDNs and Acknowledgments To access an MDN after sending a submission, follow the steps below.

1. Log on to the ESG using the user name and password for the account from which you sent the submissions.

2. From the **WebTrader** menu, select the “Check inbox” option. The receipts that are displayed specify the name of the submission file as part of their name.
3. Click the **Details** link next to the name of the required receipt to see its details.

To access an acknowledgment after sending a submission, follow the steps below.

1. Log on to the ESG using the user name and password for the account from which you sent the submissions.
2. From the **WebTrader** menu, select the “Check inbox” option. The messages with “.ack” or “.txt” extensions are the acknowledgments from Centers for submissions. The message name before the extension denotes the Core ID generated by the Center for the submission.
3. Click on the name of the required acknowledgment to see its details.

ELECTRONIC REGULATORY SUBMISSIONS AND REVIEW (ERSR)

The ERSR Web page (<http://www.fda.gov/cder/regulatory/ersr>) provides information about the electronic submission of regulatory information to the Center and its review by CDER staff. Additional guidance documents, when available in draft or final form, will be added to the Web page.

Submission of Electronic Documents (June 7, 2004)

- Send all electronic submissions (except ANDAs) to
5901-B Ammendale Road
Beltsville, MD 20705
- Send ANDA submissions to
7500 Standish Place, E-150
Rockville, MD 20855

Electronic Regulatory Submissions

General Considerations. CDER and CBER have copublished a guidance document called *Guidance for Industry: Providing Regulatory Submissions in Electronic Format—General Considerations* (<http://www.fda.gov/cder/guidance/6719.fnl.htm>). This document provides general information about the electronic submissions process.

Note: In the general considerations guidance, we recommend the following: Digital Tape—Digital Equipment Corp. DLT 20/40 and 10/20-GB format using OPENVMS with VMS backup or NT server 4.0 with NT backup or backup exec.

Since the release of this guidance, there have been some changes in CDER. First, we are currently not able to accept tapes using OPENVMS with VMS backup. Second, we are able to use 35/70 DLT tapes. We are not, however, able to handle 40/80 DLT tapes. We are working on an update to this guidance and are planning to add this information accordingly. (Posted March 1, 2001) Since the above posting on March 1, 2001, CDER has now been able to handle 40/80 DLT tapes, although we prefer 35/70. CDER cannot process DLT tapes that have been prepared by using the backup applet included with the Windows 2000 operating system. It is recommended that systems running Windows 2000 use backup exec to produce the DLT transport tape for CDER. (Posted September 28, 2001)

For more information on ERSR guidance documents, please contact Randy Levin at randy.levin@fda.hhs.gov.

ANDAs. Information on electronic data sets that accompany an ANDA submission:

You may now submit ANDAs in electronic format in place of paper. We have placed the ANDA on public docket 92S-0251 as a submission acceptable in electronic format as allowed under 21 CFR Part 11. It should be noted that Part 11 requires that data sets provided in electronic format and used in the review process meet the requirements for archiving, i.e., protection of those records to enable their accurate and ready retrieval throughout the records retention period.

Electronic data sets, including those accompanying a paper submission, cannot be considered as official and used to support the application if they are submitted in a file format that is not archivable. As FDA and industry progress in meeting the goals of use of electronic submissions, compliance with electronic submission regulations will be expected. Typically, electronic data sets accompany an ANDA to support the review of bioequivalence studies. With the implementation of the guidance for industry Providing Regulatory Submissions in Electronic Format—ANDAs (June 2002), the submission of these data set records for use in the review should be in archivable format. At this time, the archival data set format is SAS Transport. (Posted July 15, 2002)

NDAs. Please refer to Providing Regulatory Submissions in Electronic Format—Human Pharmaceutical Product Applications and Related Submissions.

Carcinogenicity Data. An example of a SAS transport file for carcinogenicity data set is available. This is a self-extracting ZIP file that will be loaded to your C drive. If you download this file, the path to the example is: C:\WINDOWS\TEMP\example\N123456\pharmtox\datasets\101.

For more information on carcinogenicity data, please contact Karl Lin at karl.lin@fda.hhs.gov.

Providing Digital Electrocardiogram (ECG) Data

Why The FDA is interested in having access to ECG waveform data collected during the course of “definitive” studies on drug effects on ventricular repolarization and annotated for interval measurements. The basis for this interest is described in detail in the concept paper “The Clinical Evaluation of QT Interval Prolongation and Proarrhythmic Potential for Non-antiarrhythmic Drugs,” jointly authored by the U.S. and Canadian regulatory authorities and discussed at a joint FDA/DIA meeting in January 2003.

How In 2004, the FDA announced its intent to accept annotated ECG waveform data in electronic format [extensible markup language (XML)] following the Health Level Seven (HL7) Annotated ECG Waveform Data Standard (aECG) accredited by the American National Standards Institute. You can find more detailed information on the aECG message standard and supporting materials by visiting the HL7 Version 3 ECG page and following the “Link to ECG Annotation Message Review Material.” To facilitate access to the aECG data, FDA has entered into a Cooperative Research and Development Agreement with Mortara Instruments to develop and implement a digital data warehouse to collect, store, and archive aECG data from controlled clinical trials. FDA reviewers have access to this data warehouse to support their assessment of the risk of new drugs.

You can upload data to the warehouse for FDA access at the Mortara ECG Warehouse. For questions, contact the project manager in the appropriate review division.

Drug Master File (DMF). Refer to the Guidance for Industry “Providing Regulatory Submissions in Electronic Format—Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications” for information on the submission of electronic DMFs.

For more information on electronic submissions for DMF, please contact CDER at esub@fda.hhs.gov. General DMF questions may be sent to dmfquestion@cder.fda.gov.

INDs. On March 26, 2002, the FDA published final guidance on the submission of INDs in electronic format to the CBER (<http://www.fda.gov/cber/gdlns/eind.pdf>). Once the IND submission to CBER is posted on public docket 92S-0251, we will be capable of accepting INDs submitted to CBER in electronic format without paper copies. At this time, we are not extending this to INDs submitted to CDER.

The electronic IND guidance leverages the current Biologics License Application /NDA guidances and the experience set from CBER’s eIND pilot program. This guidance features PDF tables of contents, road-map files, and a folder structure that enables the reviewer to easily access and review documents. We expect the experience of receiving the IND applications and amendments with or without media, featuring an electronic signature, as well as the

review of these electronic INDs submissions to help the FDA further other electronic submission initiatives.

In the future, we plan on upgrading the electronic IND filing and review process to include the use of XML-based technology. We are currently working toward accepting the electronic CTD using XML for marketing applications and will build on this to accept XML-based electronic INDs. Once this is completed, we will then issue draft guidance that incorporates the XML-based technology for all INDs including those submitted to CDER. We hope to have XML specifications for electronic INDs available in 2003.

- Federal Register notice for the public meeting to discuss the cumulative table of contents for the IND. Optional format: PDF. (Posted December 29, 2000)
- Agenda for the *Electronic Investigational New Drug Application: Cumulative Table of Contents (CTOC) Public Meeting*. (Posted January 22, 2001)
- *Electronic Investigational New Drug Application: Cumulative Table of Contents (CTOC)* (Posted December 6, 2000). This Web page provides technical information for an upcoming public meeting to discuss the possibility of a cumulative table of contents in XML for the electronic IND.

Launch Material and Other Submissions to the Division of Drug Marketing, Advertising, and Communications (DDMAC)

- *Draft Guidance: Providing Regulatory Submissions in Electronic Format—Prescription Drug Advertising and Promotional Labeling*. Optional format: PDF. (Issued January 2001, Posted January 30, 2001)

NDAs

- *Regulatory Submissions in Electronic Format; General Considerations*. (Issued January 1999, Posted January 27, 1999)
- MaPP 7600.7 Processing an Electronic NDA (Issued May 31, 2000, Posted June 5, 2000)
- Sample Electronic NDA Submission

Postmarketing Adverse Events Reporting

- *Guidance for Industry Providing Regulatory Submissions in Electronic Format—Postmarketing Expedited Safety Reports*. Optional format: PDF. This guidance document assists applicants making regulatory submissions in electronic format to CDER and CBER. (Issued May 2001, Posted May 25, 2001).

- *Postmarketing Expedited and Periodic Individual Case Safety Reports.* This allows for voluntary electronic submission of all postmarketing individual case safety reports, whether expedited or periodic, in electronic format in place of paper.
- AERS. A pilot program for electronic submission of individual case safety reports is now being conducted with pharmaceutical manufacturers with approved products. The format follows the International Conference on Harmonization (ICH) standards. For more information on the ICH, please contact Timothy Mahoney at mahoneyt@cderr.fda.gov.
- For more information on the proposed electronic submission of individual case safety reports, see 63 *FR* 59746, Advanced Notice of Proposed Rulemaking for *Electronic Reporting of Postmarketing Adverse Drug Reactions*, published on November 5, 1998.

Electronic Review

Electronic Document Room (EDR)

- The EDR is an extension of the central document room. We perform a check on each submission sent to the EDR for file formats used and for integrity of bookmarks and hypertext links.
- NDA Conformance Checklist (February 22, 2000)

Secure e-Mail and the FDA ESG. e-Mail is in widespread use within CDER and industry. Secure e-mail between CDER and industry is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). Secure e-mails should not be used for formal regulatory submissions (for example, NDAs, INDs, amendments, and supplements).

Formal regulatory submissions can be securely submitted to CDER via the FDA ESG. For more information on the FDA ESG, see <http://www.fda.gov/esg/default.htm>.

For more information on establishing a secure e-mail link with CDER, contact Wendy Lee at wendy.lee@fda.hhs.gov.

Division Files System (DFS). DFS is the cornerstone of the administrative management of files initiative. It provides document management, tracking, archiving, and electronic signature capabilities for internally generated review documents. It also provides search and retrieval capabilities for final versions of internally generated review documents.

DFS is being developed incrementally. The first phase focuses on building an electronic repository for final review documents and for capturing signature information. The review documents tracked and saved by DFS are associated with regulatory submissions in the Centerwide Oracle Management Information System (COMIS). Future phases of DFS will include an update of COMIS

assignments when the author signs the review in DFS. Reviewers use DFS to check in final review documents, to route them for sign-off, to sign off on them electronically, to automatically store review documents in the electronic repository, and to find and view documents stored in the DFS electronic repository.

The DFS is a graphical user interface software application that has the look and feel of most Windows-based applications. DFS uses standard Windows features, such as icons, drop-down menus, buttons, scroll bars, and dialog boxes.

Reviewer Training

- **Electronic Submissions Training.** Instructs reviewers on how to search for a specific NDA via the EDR Intranet site and to map the drive path of the folder. Acrobat Exchange is then used to open, navigate, view, follow links, create electronic notes, and copy and paste text, tables, and graphics into other applications from a sample electronic NDA.
- **Electronic Data Analysis Training.** Instructs reviewers on how to access NDA data in SAS Transport format via the EDR and to convert the files to formats that can be used with a variety of software packages. **NDA Electronic Data Analysis Training (NEDAT)** incorporates the use of the SAS System Viewer, Stat/Transfer, and JMP to convert the data and perform basic analysis. Additional introduction to JMP courses that discuss analysis of adverse events, exposure, efficacy, lab, and demographic data are also available.
- **Creating PDF Reviewer Documents.** Instructs reviewers on how to create a PDF version of a review document that maintains the formatting of the original MS Word document. Instruction covers fonts, paragraph, page, and section formatting are needed prior to converting an MS Word review document to the PDF archiving standard used in the DFS. Adobe Acrobat 4.0 is then used to convert the document to PDF and to open, view, and enhance the PDF review document.
- **JMP.** An introduction to JMP teaches reviewers how to use JMP to review electronic data. Users learn how to use a variety of JMP functions to analyze electronic data, with a specific focus on adverse event, laboratory, exposure, and efficacy data. Basic functions of summary tables, graphs, statistical tests, and the formula calculator are covered. The course is taught in the computer lab with hands-on instruction. Prior completion of the **NEDAT** course or familiarity with electronic data sets or both are recommended. Although primarily geared toward the clinical reviewer, the course provides useful instruction for reviewers of all disciplines.

Helpful Links

Docket. The Agency established the Electronic Submissions Public Docket number 92-0251 to provide a permanent location for a list of the Agency units that are prepared to receive electronic submissions, as well as a list of the

specific types of regulatory records that can be accepted in electronic format (62 FR 13467, March 20, 1997).

PDF Format. PDF is an open format developed by Adobe Systems. Additional information is available at <http://www.adobe.com>.

SAS Transport File Format. We are able to archive data sets in SAS XPORT transport format, also called version 5 SAS transport format. This is an open, published file format developed by SAS Institute. For additional information, see the SAS Institute's Standards for Electronic Submissions and SAS XPORT transport format Web site.

Technical Assistance. For more general information regarding the preparation of submissions in electronic format, please contact the Electronic Submissions Coordinator at esub@fda.hhs.gov.

Recent Presentations

- 42nd Annual Meeting of the Drug Information Association, June 18–22, 2006, Philadelphia, PA
- Gensinger, Gary, MBA, Director, Regulatory Review Support Staff, Office of Business Process Support; *Standards and Successful Document Creation*
- Ventura, Virginia, Regulatory Information Specialist, FDA Office of Business Process Support; *eSUBS and eCTDs: Practical Advice and Pitfalls to Avoid*
- eCTD Tutorial, April 22, 2005, Rockville, MD, Agenda and Presentations (April 26, 2005)
- Electronic Submissions and Data Standards Quarterly Update, March 4, 2004, Rockville, MD, FDA
- Update on Standard for Exchange of Nonclinical Data, Thomas Papoian, PhD, CDER
- Overview of the eCTD Guidance and Its Implementation, Gary M. Gensinger, MBA, CDER
- Introduction to SDTM v3.1, Norman Stockbridge, CDER
- Study Tagging File Workshop Thomas Selnekovic, CDER, February 26, 2004
- eCTD Workshop, February 26, 2004, Randy Levin, MD. CDER
- Public Meeting on Clinical Data Interchange Standard Consortium Version 3 Submission Data Standards and Electronic Case Report Tabulations, October 2, 2003, Rockville, MD (Posted October 7, 2003)

- Future of Case Report Tabulation Submissions, Randy Levin, MD,
- Web Submission Data Manager: Demonstration, Steve Wilson, DrPH.
- 2003 Annual DIA Meeting, June 2003, San Antonio TX (Posted July 15, 2003)
- DIA Annual Clinical Data Management Meeting in Philadelphia held on March 31, 2003.
 - Data Standards Update, Randy Levin, MD
- DIA Electronic Document Management Meeting, February 13, 2003 (Posted February 24, 2003)
 - DailyMed Initiative: Enhancing Patient Safety Through Accessible Medication Information, Randy Levin, MD
 - FDA Data Council Initiatives, Randy Levin, MD
- *Electronic Submissions to the FDA*, Randy Levin, MD, Fifth Annual Electronic Document Management Conference, September 23, 2002 (Posted November 14, 2002)
- *Impact of Regulations on Data Management Practice*, Randy Levin, MD, DIA Twelfth Annual European Clinical Data Management Conference, November 5, 2002 (Posted November 14, 2002)

Other ERSR Links

- CDER Electronic Records; Electronic Signature Regulations. This page provides links to pertinent *Code of Federal Regulations* and Federal Register documents.
- ERSR Agency Charter. Federal Register–Electronic Records; Electronic Signatures, Final Rule, March 20, 1997.