

Getting started

with the FDA's electronic submissions gateway

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Abstract

At the end of June 2009, the US FDA stopped accepting Establishment Registrations and Product Listings on paper. Instead, all such submissions are now required to be filed via the Electronic Submissions Gateway (ESG). Companies with products to list and companies that wanted to register with the FDA as pharmaceutical or medical device establishments had a choice: outsource the work or set up an in-house capability. This article describes the processes and potential pitfalls of setting up an in-house ESG. Progressing from filing the letter of non-repudiation, to implementing the computer software, through submitting documents via the ESG, it illustrates the practical experiences of regulatory affairs professionals during the past year. Additionally, this article provides contemporaneous information on the FDA Centers and documents that the agency accepts, as well as a brief discussion of the FDA's electronic Common Technical Document (eCTD).

Introduction

The US FDA's Electronic Submissions Gateway (ESG) is an agency-wide mechanism for accepting electronic submissions for review. It is the first portal through which submissions travel to their targeted FDA Office or Center. The ESG does not open or review submissions. Documents are automatically routed to the chosen Office or Center. Receipts and acknowledgements sent to the sender via the ESG verify good reception of the electronic submission, not its acceptability to the receiving Office or Center.¹

Some submissions, such as establishment registration and listing of marketed products and safety reporting, are required to be made via the ESG. Each FDA Office or Center has specific guidelines for preparing electronic submissions and will only accept specific types of submissions for the ESG or other electronic formats. Prior to preparing an electronic submission, the user should refer to Center-specific submission preparation guidelines. There are some parts of the FDA, such as the Office of Orphan Products Designation, that are not yet equipped to receive electronic submissions via the ESG, but which will accept electronic submissions on digital media such as CD.

WebTrader

Prior to registering for an ESG account, one must determine which submission option to use, the FDA ESG Web Interface (WebTrader) or the AS2 Gateway-to-Gateway. This determination is based on types of submissions to be transmitted, infrastructure capabilities and business considerations. The WebTrader is the low-cost option and has fewer set-up requirements than the Gateway-to-Gateway option.² Figure 1 illustrates the process for obtaining a WebTrader account. During the 2009 implementation, many companies found that establishing their accounts was more time-consuming than they had envisaged. Interviewees reported spending four to eight months establishing and testing their WebTrader accounts.

We recommend several preparatory activities precede the formal request to the FDA. Procure a DUNS number for your establishment if required (one DUNS number per address). Set up a digital certificate. The digital certificate is required in order to use an electronic signature and provides authentication, confidentiality, integrity, and non-repudiation of data.³ Prepare an electronic submission. This submission does not need to be guidance-compliant (the submission will not be reviewed by the FDA), but should be representative of the file types that would be submitted in a typical submission (ie, a mixture of PDF, text files, MS Word files, etc.). Set up the computer system that will do the submissions through ESG; the operating system should be Windows XP and the Java SE runtime environment (JRE) 5.0. You will need a browser; ESG is compliant with Internet Explorer 6, 7, 8 or Firefox 2.0.x. The digital certificate and WebTrader account are specific for the computer on which they are set up. There are several documents available on the FDA website that aid in setting up a WebTrader Account.^{4,5}

Once the DUNS number is available, the digital certificate is set up, and the computer is configured, submit a Letter of Non-Repudiation to two separate locations within the FDA.² Submit these letters in paper form, on company letterhead, and signed with a traditional handwritten signature.^{4,5} The letter certifies that the electronic signature is the legally binding equivalent of a traditional handwritten signature.

A request for the ESG WebTrader test account should be sent to esgprep@fda.gov providing the company name, user's name, phone number and submission option (WebTrader). The FDA's response will outline the steps for completing registration and for setting up the WebTrader test account. This email will contain the instructions for installing Java's JRE and JCE software and details for configuring the firewall. Once the final software adjustments are made and

a test submission is successfully uploaded through the test ESG, a production account may be requested.⁶ The process for obtaining a production account is the same as for the test account.

Structured product labelling

In the *Federal Register* of 11 December 2003 (68 FR 69009), the FDA published final regulations requiring that the content of labelling be submitted to the FDA electronically. New drug applicants who submit content of labelling to the FDA as part of a marketing application are required to use the structured product labelling standard (SPL) in extensible markup language (XML).⁷ This trend toward standardisation of the package insert reached a milestone of sorts when the FDA instructed that all drug establishment registrations and drug listings must be in SPL after 30 June 2009. The FDA offered courses on SPL4 to the industry in 2009, published a Guidance Document,⁸ and provided a page of instructions on its website.⁹

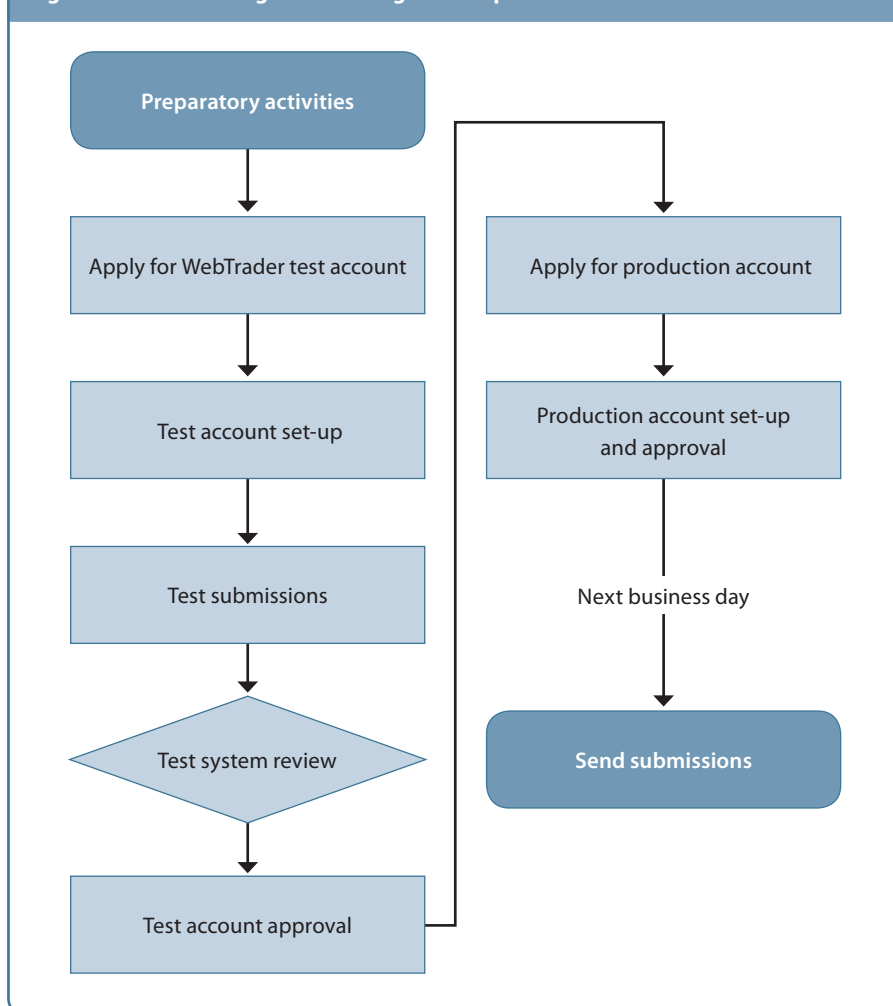
Safety reporting

Both the Center for Biologics Evaluation and Research (CBER) and the Center for Drug Evaluation and Research (CDER) accept electronic submissions of adverse events into the Adverse Events Reporting System (AERS). Individual Case Safety Reports (ICSRs) must be created in the XML format using a standard structure prepared in accordance with the International Conference on Harmonisation-E2B (ICH E2B) data elements. Instructions for submitting ICSRs in the XML format are found in "Steps to Submitting ICSRs Electronically in the XML Format."¹⁰

The Center for Devices and Radiological Health (CDRH) also utilises the ESG to receive adverse events. The electronic Medical Device Report (eMDR) application uses the Health Level Seven (HL7) ICSR standard for the reports. Two options for submitting eMDRs are available:

- 1 FDA eSubmitter (formerly CeSub), a free downloadable application, allows submission of eMDR reports one at a time for low volume reporters. The eSubmitter contains data elements of the MedWatch Form 3500A which are manually entered and then packaged as an HL7 ICSR message.
- 2 High volume and frequent reporters do not require the eSubmitter. The eMDRs are created directly from adverse event information in the reporter's system and formatted as a HL7 ICSR.¹¹

Figure 1: Schematic diagram of the registration process for the ESG WebTrader account



Electronic Common Technical Document

The eCTD format is acceptable for NDA, 505(b)(2), BLA, ANDA, IND and DMF submissions. However, it is not acceptable for submissions for 510(k)s, PMAs, veterinary products submissions, or orphan drug designation requests. There are only a few areas where submitting an eCTD through the ESG differs from submitting an eCTD to other health authorities. In this regard, eCTD Module 1, containing regional specific administrative information, is critical because it is used to process the submission and assign it to the correct FDA division. It also contains the information needed for managing the application. Module 1 identifies to the automated system the user's application and sequence. If the specifications are not followed, the submission will fail to be validated and will not be reloaded for review. This is the only place in the eCTD document where the application administrative identification information is provided in machine-readable XML format.^{12,13}

In Module 1, forms should be completed using the fillable form. (Any use of non-fillable forms will require manual review and cause delays in getting to the reviewer.)

The us-regional.xml should contain a numeric digit application number and a submission sequence.

Submissions are validated at three levels. First, the Automated Submission Receipt (ASR) will perform an initial validation, activate the eCTD validation, load the submission into the tracking system and notify a regulatory project manager.¹⁴ At the second level, the eCTD validation tool identifies and rates the types of errors according to specifications defined in www.fda.gov/cder/regulatory/ersr/validation_specs.htm. The third level of validation occurs through Division quality checks. This validation will check the table of contents, hyperlinks/bookmarks, datasets, and granularity in which errors may interfere with the review. Rejection of a submission occurs

Electronic submission gateway users should check to ensure their submissions are sent to the correct FDA Center. This is a very common problem, and all submissions sent to the wrong Center are automatically rejected

at the ESG level. After validation is complete, a message will be sent to the user's inbox.¹⁵

Although this process may appear to be fairly straightforward, many errors continue to plague users.^{16,17} Common errors to eCTD submissions using the ESG include the following:

- Duplicate submissions. Each click sends a submission. A duplicate sequence is determined by the sequence number in the us-regional.xml. The first sequence is accepted, but subsequent submissions of the same sequence number are rejected. Acknowledgements of submissions will generally take one to four hours, depending on their size. To see the acknowledgement, the user must refresh the computer screen.
- Missing files can cause errors. It is important to verify content before sending.
- The user should check to ensure that the submission is sent to the correct FDA Center. Interestingly, this is a very common problem. All submissions sent to the wrong Center are automatically rejected.
- The us-regional.xml file must be included. This is an essential file. Without this, it is impossible to process the submission.
- Submissions with empty folders or unreadable media will be rejected.
- A submission with an incomplete or missing application number, or more than one sequence number, will be rejected.
- Certain characters such as a space, a forward slash (/) or backward slash (\) are not permitted in naming submission files and directories. The list of illegal characters can be found in the FDA Electronic Submissions Gateway User Guide.² When an illegal character or space is found, the submission is put into a queue for manual processing, which causes delays in getting information to the reviewer.

The most frequent complaint among ESG users is the slow loading speed for some larger submissions. The ESG appears to be the slowest in the late afternoon, particularly Friday afternoons. Because the inbox size affects login performance, it is important to have fewer than 20 submissions in the user's WebTrader

inbox. Submissions appear in the first column of the display in the Inbox under the column heading "Submission name." To allow time for receipt when sending submissions larger than 7.5 GB, it is important to begin well before the target submission time, preferably the prior evening. The receipt date refers to the time the submission is received. Official receipt hours are business days 8:00am–4:30pm EST (GMT -5) and submissions received outside of these hours are received the next business day.^{12,13}

Summary

Implementation of the ESG throughout is ongoing. This article delineates some of the processes and pitfalls encountered during the first year that the authors used the ESG system. Readers are well advised to confirm current ESG specifications and requirements with both ESG staff and the FDA Center or Office before undertaking filing via the ESG. That is, expect that processes and rules will continue to evolve for the foreseeable future.

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