

The eCTD Submission Process: Tips and Tricks for Drug Development Success



By Robert Labriola & Evan Richardson

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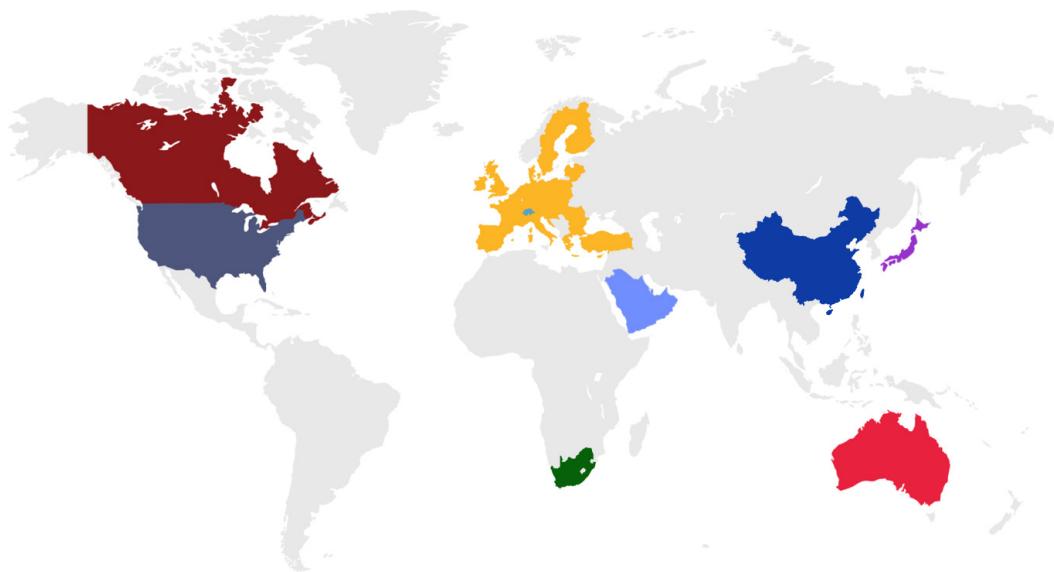
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INTRODUCTION

Regulatory agencies worldwide increasingly rely on standardized formats such as the electronic Common Technical Document (eCTD) for submissions to streamline the process for evaluating investigational drugs.

The eCTD, an electronic version of a Common Technical Document (CTD), is used to submit regulatory information such as applications, reports, amendments, and supplements to agencies such as the FDA's Center for Drug Evaluation and Research (CDER), the Center for Biologics Evaluation and Research (CBER), Australia (TGA), Switzerland (Swiss Medic), Japan (PMDA), China (NMPA), Health Canada, and the European Medicines Agency (EMA). Regulatory submissions must conform to the eCTD format to be successfully received and reviewed by health authorities.¹

This has allowed for greater efficiency in submissions and reviews by improving clarity and consistency. Although using eCTD has made the process more efficient, getting documents in the proper format for submission may not be straightforward to someone unfamiliar with it.



A BRIEF HISTORY OF THE eCTD

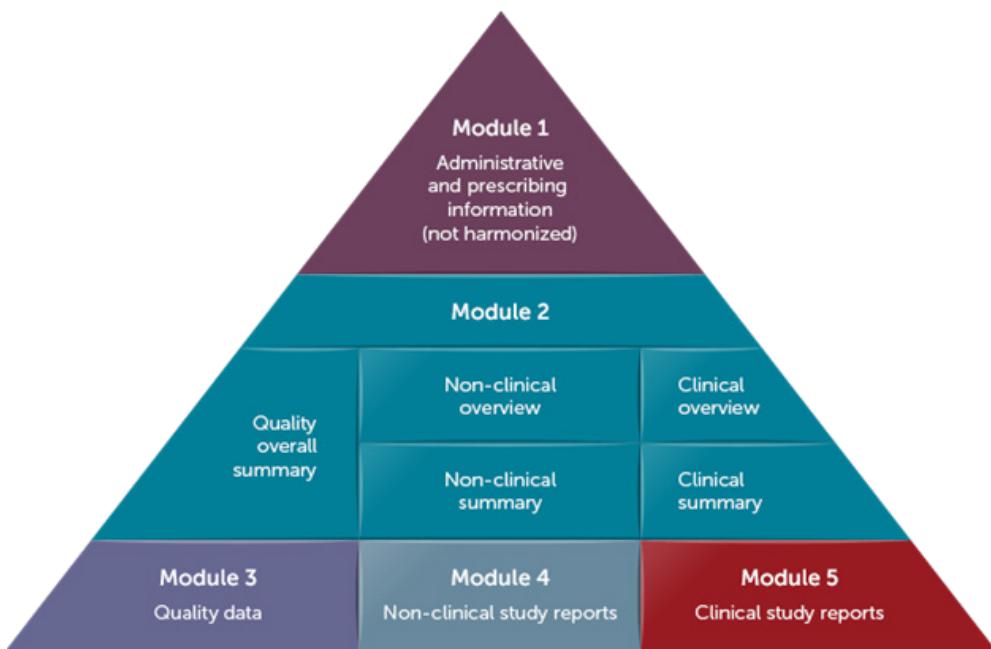
The concept of the eCTD was developed by the International Conference for Harmonization (ICH) Multidisciplinary Group 2 Expert Working Group.² This working group is an international organization that develops international standards (ISOs) and provides guidance for the pharmaceutical industry on testing requirements and methodologies. The group provides recommendations on how to conduct safety testing of new drugs and how to interpret the results of these tests.

Their idea was that every health authority globally could implement CTD (eventually eCTD) to streamline the regulatory review of new drugs and potentially all regulated products.

The eCTD contains five modules:

1. Administrative information and prescribing information
2. Common technical document summaries
3. Quality
4. Non-clinical study reports
5. Clinical study reports

Module 1 is usually considered separately since it contains documents that are specific to each region. Modules 2-5 are the common modules of the eCTD. The idea was that once a Sponsor develops the content for modules two through five, they could reuse it for submissions wherever eCTD is accepted: the US, Canada, the European Union, etc.⁴



WHY IS USING THE eCTD FORMAT IMPORTANT?

The eCTD enables the submission of regulatory information in a standardized format, which makes it easier for agencies to access and review the data. Regulatory agencies are increasingly accepting them as a standard submission format, and with many agencies eCTD is mandated (US FDA, EU EMA, Health Canada, and China, to name a few). The UK health authority, MHRA, accepts eCTD through a recently established portal. Using an eCTD format for submissions provides many advantages:

- It can make the review process by the agency more efficient, as all the required documents are compiled in a standardized way.
- It helps to ensure that submissions are complete and meet all necessary requirements.
- It helps to speed up the review process.
- It provides a better way to keep track of submissions and their status.

However, there are also some disadvantages to using an eCTD format for submissions that you should also be aware of:

- It can be time-consuming to reformat legacy documents into the eCTD format.
- There is a risk that some of the original formatting could be lost in the conversion process.
- Publishing software is required for preparing the submission.

Overall, the advantages of using eCTD outweigh the disadvantages, and the resulting process is more streamlined, which saves time and money long term.

THE KEY TO A SUCCESSFUL eCTD SUBMISSION

Preparing an eCTD requires careful planning and organization. It is important to produce a well-organized document that adheres to the eCTD guidelines. This might seem simple; however, it can be a rather complex technical process. A lack of expertise in medical writing and regulatory publishing can increase the risk of submission rejection.²

How to submit an eCTD to the FDA

Before submitting an eCTD, learn as much as possible about the process. Familiarizing yourself with eCTD and the submission gateway before you start will save you time and frustration later.³

To submit an eCTD to the FDA, complete the following steps:

1. Register with the FDA's Electronic Submissions Gateway
2. Create a user account
3. Obtain a submission identification number
4. Prepare your eCTD according to the FDA's specifications
5. Send a sample submission to the FDA (optional)
6. Submit using the Electronic Submission Gateway

A few key elements comprise a successful eCTD submission. First, all the required documents must be included and correctly formatted according to the eCTD guidelines. Secondly, the submission must be complete, meaning all sections must be completed error-free and include all required information. Lastly, the relevant authorities must review and approve the submission before it can be considered complete. The submission will likely be rejected if any of these elements are missing or done incorrectly.

RTFs: HOW THEY HAPPEN AND HOW TO MITIGATE YOUR RISK

The FDA issues a refusal to file (RTF) letter to sponsors when it determines that a submission isn't sufficiently complete to permit a substantive review. An RTF letter generally indicates that the submission contains deficiencies that preclude the agency from beginning its review. In some cases, an applicant may be able to revise the submission to address the deficiencies identified in the RTF letter and resubmit the application for review.

Here are two common regulatory pitfalls that can invoke an RTF.

- The submission fails based on technical errors: When the FDA receives a submission, they conduct a technical review to check it for errors. If the submission has serious validation errors (High Errors), they will reject it immediately. For example, the folder structures, files, or XMLs don't meet the validation criteria.
- The submission fails based on content: Examples of this type of failure are not including the required case report forms, not putting data packages in the correct CDISC (Clinical Data Interchange Standards Consortium) format, or forgetting to include an integrated safety summary report, which summarizes all the safety information in the submission.⁹

During the transition period from paper submissions to eCTD, the agency issued many RTFs as sponsors learned how to implement processes for complying with this regulation.

ENSURING HIGH-QUALITY SUBMISSIONS

By embracing regulatory operations best practices, you can avoid the risks of failing to meet eCTD standards and thus incurring an RTF from the agency.

Here are some best practices to ensure that your eCTD submissions are high quality:

- Make sure that the documents are well-written, organized, and follow the proper format.
- Include all the required documents in the submission.
- A qualified individual should review the submission, and a technical validation should be performed before sending it to the regulatory authority.

SATISFYING REGIONAL REQUIREMENTS

By embracing regulatory operations best practices, you can avoid the risks of failing to meet eCTD standards and thus incurring an RTF from the agency.

eCTD requirements differ between regions in two major ways:

- Differences in module 1 content
- Validation criteria

eCTD module 1 contains regional requirements: the prescribing information, packaging, and local government forms (e.g., PDUFA user fees in the US).

Each region has its submission specifications and requirements. For example, the European Union can accept submissions using their "centralized procedure," which grants approval to market a drug in all EU countries.

Additionally, each region has their own validation criteria by which they scrutinize submissions for errors. So, every time a country or region updates its validation criteria, or local requirements, update your version of the submission validation software for that specific country or region.

DO YOUR HOMEWORK TO GET IT RIGHT THE FIRST TIME

Many sponsors have difficulty getting their eCTD submissions processed. For example, an organization consisting of experienced scientists from academia had problems during the document preparation process, resulting in delays. The organization's experience was mainly in disease research, and they didn't spend much time focusing on eCTD. Their drug candidate was in phase three trials and had received significant venture capital investment.

Getting documents into an eCTD format using templates was a challenge for them. Their staff was writing reports without following the eCTD format. And they also weren't collecting the data from studies to conform to eCTD requirements.

By not having their submission conform to eCTD standards, this sponsor could risk a delay in submission, which would lead to a delay in approval. This obviously puts pressure on financing the business, treating patients, and maximizing drug patent length. In addition, receiving an RTF from the FDA adds to the time and cost of developing a drug by delaying its review. Submissions can fail, sometimes within just minutes of arriving at the agency.¹

FREQUENT eCTD QUESTIONS

What is the process for getting a submission into the eCTD format, and when should we start?

The first step is to get your submission documentation into the format specified by eCTD templates. Regulatory and medical writing teams usually write all the clinical and non-clinical studies in content templates that format everything according to eCTD regulations. These eCTD authoring templates should be used for any report planned for a regulatory filing, no matter how far off the submission deadline may be.

Once the documentation is in the correct format, the content should be approved by subject matter experts and regulatory operations. Once approved, it's transferred to the publishing team, who starts the submission compilation. This involves creating PDF files, adding navigation aids (bookmarks and hypertext links), and uploading them to the eCTD publishing software. Once the publishing team has performed its process, the eCTD files and sections should be reviewed again by the subject matter experts.

What is the XML backbone, and how do we create it?

The publishing software completes two major tasks automatically. First, it creates the proper folder and subfolder structure that organizes the eCTD documents by modules. It also auto-generates an XML backbone.

XML (Extensible Markup Language) is used to create structured documents in a format that is readable to both humans and machines. It is important in an eCTD submission because it allows for the exchange of data between different systems, which is essential for the electronic submission of regulatory documents. XML also enables structuring data in a way that makes it easier to process and manipulate.

XML allows the eCTD viewing software to load the application and structure the files in their proper order over the life cycle. The XML backbone provides required metadata as well as document life cycle operators, which are loaded into the eCTD viewing tool.

Without an XML backbone, your submission will fail the regulatory agency's validation software. Thus, the health agency reviewers will not review your submission because it won't load into the review software.

What do people mean when referring to a submission's "metadata"?

Metadata in the case of eCTD submissions refers to structured data. Think about unstructured data as a PDF file or a Word document. Metadata provides essential information about the submission's structure, content, and format. This information helps reviewers to understand the submission and make informed decisions about its content. Additionally, metadata can be used to generate summary reports, track changes over time by a reviewer, and group and view all previously submitted information related to that metadata.

Large submissions contain thousands of documents with unstructured data. The eCTD message that is sent contains structured data as well. Some of the information entered as metadata with submissions includes the application types, sequence types, sequence numbers, Dun & Bradstreet numbers, the regulatory contact name, and their phone numbers. The regulatory operations will add this information through the eCTD publishing software.

The role of metadata will likely be expanded with future versions of eCTD as eCTD V4 is implemented and potentially impacts the identification of medicinal products (IDMP) on Structured Product Labeling (SPL).

HOW CAN USING AN eCTD SUBMISSIONS VENDOR HELP?

An eCTD submissions vendor provides software and services to help companies prepare and submit regulatory filings in the correct eCTD format. They typically help with every stage of the eCTD submission process, from authoring and assembling documents to converting them to the correct format and submitting them electronically to the regulatory agency.

You may be wondering if working with an eCTD submissions vendor is right for you and your company. After all, why spend money to have someone do it for you when you can do it yourself? There are many good reasons not to do it yourself.

Our time is valuable and outsourcing complicated and time-consuming tasks to an expert is a common business practice that saves money in the end. Putting together an eCTD submission yourself can be challenging. If you're unfamiliar with the process, an eCTD submissions vendor can help ensure compliance with regulatory guidelines and standards.

CHOOSING AN eCTD SUBMISSIONS VENDOR: YOUR COMPLETE CHECKLIST

Once you decide to get help with your eCTD submissions process, the next step is to select the right electronic submission services vendor for your organization. This selection process can vary greatly. Some organizations have rigorous prescribed procedures, while others use a less formal, less structured approach. Choosing a vendor requires balancing between desire/presumption and the ability to make things happen. You need to choose a vendor who will help you cross the regulatory submission "finish line." They must be current on eCTD requirements and understand the ever-changing regulatory landscape. Here are some things to look for during your search.⁵

A strong company overview including solid financials

Work with a company with market leadership and broad expertise in the industry. This includes sound financial health and a track record of success, especially in the regulatory operations and submissions space. This is not the time for bargain shopping for the cheapest company you can find.

Integrated service offerings

One of the greatest benefits of using a vendor that acts as your "one-stop shop" is that you only need to use one! You need a team composed of submission experts able to support publishing through technical expertise and consultants able to guide you through the whole process. Teamwork, financial accounting, partnering, and cohesiveness are important factors that affect enterprise characteristics.

Strong credentials are a must

When selecting a vendor, look for one with a strong reputation and references that verify their quality. Case studies, testimonials, and clients you can contact as references are all important assets that can direct your decision-making.

Specialized consulting and regulatory expertise

The regulatory operations team should have deep expertise in the submission process and know how to harness technology to support it. Additionally, look for vendors that offer real-world advice on strategy and expertise on your submission type.

Round-the-clock publishing support/flexibility and scalability

It's imperative that a vendor can seamlessly move your project forward. eCTD submissions impose impending timelines with many moving parts. Look for vendors with flexible software and support services that can handle any submission challenges. They should be flexible enough to scale up or down as needed to support a submission, making it possible to meet even the most challenging of deadlines.

Clear and comprehensive contract

A clear and comprehensive contract helps to ensure that you and your submissions vendor are aware of your obligations and that the project scope is understood. The contract should outline everyone's roles and responsibilities, as well as the timeline and deliverables for the project. This can help avoid any misunderstandings or disputes that may arise during or after the submission process.

Innovative technology and an easy-to-use interface

Your submissions vendor should utilize technology that allows jobs to get done more quickly and efficiently and to the highest quality. They must provide your regulatory operations team with the eCTD software they need to efficiently publish, validate, and review regulatory submissions. This technology should save time and improve quality/accuracy while employing a simple user interface.

Efficient and speedy onboarding process

When it's time to start, it's time to start! Selecting a vendor who can smoothly onboard and ramp up quickly could make the difference between missing and meeting a regulatory submission deadline.

Templates available that support multiple eCTD jurisdictions

Creating submission-ready regulatory documents that are eCTD compliant comes with unique challenges. Companion authoring templates act as a springboard to submission success. If your vendor has templates to choose from, this is a huge plus! These templates can be used and re-used to standardize the submission components you may be struggling with. They should support the region(s) where you intend to submit, including the US FDA, Health Canada, European Medicines Agency, UK MHRA, Swiss Medic, Australia TGA, and Japan PMDA.

Strong user authentication and advanced security

It is important that your prospective vendor prioritizes security and can demonstrate that its software applications have gone through proper validation and certification. The software should be designed to be safe and secure for all your projects, including Advanced Encryption Standard (AES-256) encryption for data at rest and at transfer.

Pharmaceutical and biotech companies continue to rely on vendor use and reliance for eCTD electronic submission, and this reliance is growing. Partnering with the right vendor may be the difference between a successful or failed submission. Utilizing a vendor evaluation checklist will help you identify the provider with the right people, best procedures, and most efficient tools/technology to get the job done.

WHEN SHOULD YOU SELECT AN eCTD VENDOR FOR YOUR REGULATORY SUBMISSION?

Selecting an eCTD vendor is an important decision that can impact the success of your regulatory submission. Just as important is deciding when to make your selection. At first glance, you might think that choosing a vendor can wait until near the end of your project timeline. After all, you can't start publishing the submission until all the regulatory content has been generated and finalized, right? Wrong. Don't wait until it's too late. Here are three reasons why the earlier you engage an eCTD vendor, the better off you'll be.⁶

Reduce your team's stress level

Consider how thinly stretched you and your team will be as the target submission date grows closer. Your team will be engaged in writing, reviewing, and managing the authoring of many key components of the submission. You may be involved in things like coordinating the closeout of your pivotal clinical study, managing contract research organizations, data management, or solving a lingering Chemistry, Manufacturing, and Controls (CMC) issue. On top of all of that, you'll also be responsible for reviewing and approving the eCTD publishing work. You decided to use an eCTD submission vendor, but not selecting one until near the end of the project can lead to unnecessary stress.⁷

Get your files finalized sooner

A typical marketing application includes hundreds of thousands of pages of regulatory documents across more than a thousand individual files and can climb into the millions of pages if a significant number of large case report forms are included. While some key documents will not be finalized until the end of the project (Module 2 summaries, for example), most files to be included in the submission are usually finalized sooner, and some of them are likely available for publishing now (such as non-clinical study reports).

Take advantage of specialized experience

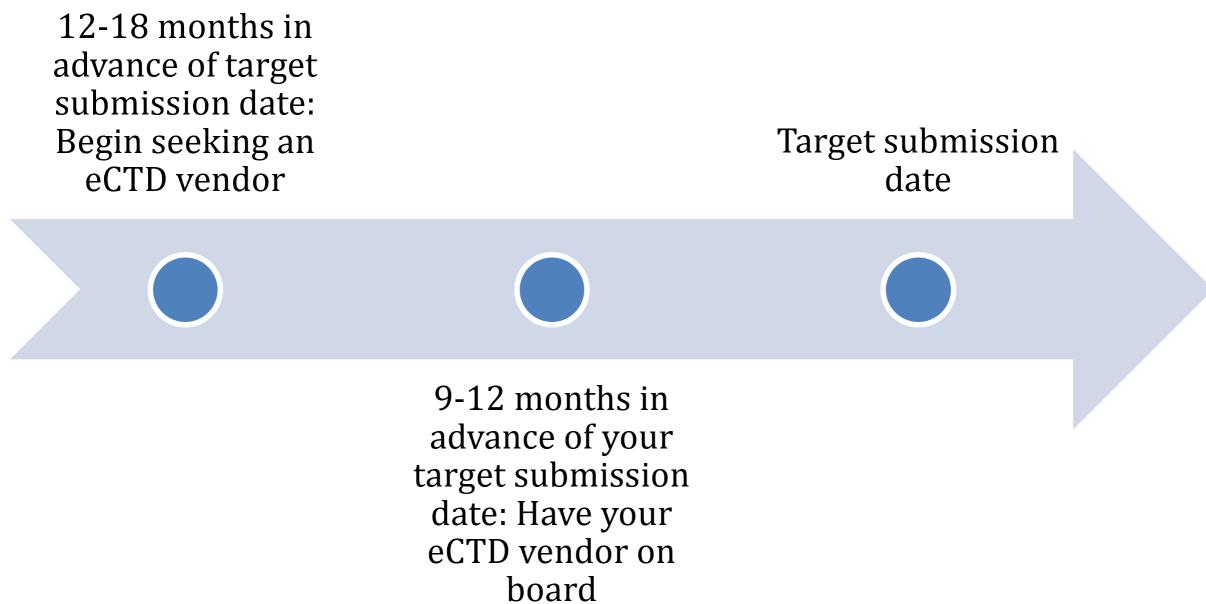
Engaging an eCTD submissions vendor earlier in the project allows them to become part of your overall project team. These team members have been through this process many times before and have a wealth of experience that will benefit you. They can recommend authoring templates to facilitate the creation of submission-ready documents. They can provide insights on how to organize your documents to facilitate easier post-approval updates. They can advise on how to structure the content within your documents to make them more navigable and "reviewer friendly." They can even help you plan how to efficiently submit the same application to multiple regulatory health authorities (FDA, EMA, PMDA, etc.). Most importantly, a good eCTD submissions vendor can help you identify and avoid common pitfalls, jeopardizing your submission timeline, and putting your overall success at risk.

When to engage an eCTD vendor

So, when is the best time to engage an eCTD submissions vendor? The right time will vary depending on the needs of your organization. For a marketing application, begin seeking an eCTD vendor 12-18 months in advance of your target submission date, with the goal of having your chosen vendor on board no later than 9-12 months in advance of your target submission date, erring on the high side for larger submissions. This timing allows for eCTD publishing to proceed at a steady pace, publishing documents as they are completed and avoiding a large bolus of work at the end of the project that could threaten the submission's success.

Figure 1.

Timeline for selecting an eCTD vendor.



THE NEXT STEP

The eCTD process makes it possible to achieve greater efficiency in submissions and reviews and improved clarity and consistency. Although it is a more efficient process, getting documents in the proper format at the correct time can be challenging.

Certara's regulatory operations experts and Global Submit technology can help you avoid the common issues that can lead to submission rejections. Our track record of success in regulatory submissions, compliance, and eCTD management can help you to increase the probability of your drug program's regulatory success.

Author Biographies



Robert Labriola

Rob has over 25 years of experience in regulatory submissions. He is involved in the production of electronic regulatory submissions to numerous health agencies at all roles and leadership levels. Rob has been with Certara for five years, where he heads up the regulatory operations team.



Evan Richardson

Evan is an accomplished, results-driven regulatory affairs professional specializing in eCTD submissions, FDA interactions, and project management. With 15+ years of experience, he has a proven track record of successful regulatory submissions to a variety of regulatory authorities.

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About Certara

Certara accelerates medicines using proprietary biosimulation software, technology and services to transform traditional drug discovery and development. Its clients include more than 2,000 biopharmaceutical companies, academic institutions, and regulatory agencies across 62 countries.

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