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Review

Electronic Regulatory Submissions

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Abstract

This document represents the Agency's current thinking on regulatory submissions in electronic format. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An elective methodology might be utilized assuming such methodology fulfils the necessities of the material resolution, guidelines, or both. This is one in a progression of direction records expected to help you while making administrative entries in electronic organization to the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER), Food and Drug Administration (FDA). This direction talks about broad issues normal to a wide range of electronic administrative entries. Now and again, the direction for one focus varies from that for the other focus due to contrasts in systems and in the PC frameworks in the focuses. We will attempt to limit these distinctions at every possible opportunity. Organization direction archives on electronic administrative entries will be refreshed routinely to mirror the developing idea of the innovation in question and the experience of those utilizing this innovation.

Keywords: Regulatory, Review, FDA, CDER, CBER.

INTRODUCTION

Introduction to Regulatory submission

Regulatory submissions are packages of information and data needed by a regulatory agency to establish whether a regulated healthcare product can progress to clinical testing or whether it is safe and effective for marketing.

A regulatory submission for a healthcare product includes any documentation or information submitted to a regulatory agency for review, for notification or in response to a request for additional information related to a healthcare product. The format can be paper or electronic, or both. The amount of information involved and its required complexity can vary significantly. A licensing application for a drug or biological product may contain hundreds of paper volumes whereas a response to an agency's question for a clarification may involve a single page. Due to the enormous amount of information presented in a marketing application, agencies are

encouraging applicants to submit applications electronically in required formats that can facilitate their regulatory review (e.g., eCTD for drugs and biologics). In Canada, for example, all premarket review documents for class III and class IV medical device licence applications and licence amendment applications are expected to be submitted in both paper and electronic formats, and the applicant must structure the format of the electronic submission to meet the agency's specifications. Be sure to monitor the regulations concerning electronic submissions as this format may soon become mandatory for your regulatory submission.[1]

Types of regulatory submissions[2]

Types of regulatory submissions can include:

- Licensing applications for drug, biologics or devices
- Clinical trial applications
- Requests for orphan drug or fast-track designations
- Requests for protocol assistance
- Responses to agency questions that arise during the review; e.g. clarifaxes, deficiency letter, requests for additional information
- *Post approval studies or commitments*

Planning for and preparing a regulatory submission

Before preparing any regulatory submission, identify the relevant regulatory requirements so that you can ensure your submission will comply.

Note that the requirements for drug and medical device submissions are quite different. Consider the following:

Who is the regulatory agency and what is the review division for my healthcare product?

What are the regulatory requirements that govern my submission?

What kind of information should be included? Is there a guidance document available that details the format and content requirements of the submission?

Where do I send the submission?

How many copies should I submit?

Should I submit the submission in an electronic format? Is that mandatory?

For hard-copy submissions, are there requirements regarding binding?

For electronic submissions, what is the acceptable data format, file size and means for submission (e.g., CD-ROM, secure gateway)

Develop a standard format or style guide for managing submissions. Submission templates should have built-in styles for headers and footers, headings, table and figure titles, and so forth. Such templates should also identify the paper size as well as the margins (both portrait and landscape) for printing and binding purposes. This is particularly important if you plan to generate global submissions, as the information can then be printed on both letter size and A4 paper and permit proper binding.[3]

As the submission should facilitate the regulatory review, organize the information so that it is easy to read and properly sectioned. Have it support navigation so the reviewer can quickly find what they need. Where applicable, consider using these elements:

1. Cover letter
2. Table of contents
3. Volume and page numbers
4. Clear headings and subheadings
5. Table and figure numbers, with accurate references to them from within the text
6. Tabs that aid quick finding of the submission sections
7. Reader-friendly font sizes, types and colours
8. Ensure that content is clearly legible and that submissions are properly bound using binders acceptable to the regulatory agency. Lastly, if any source document is in another language, ensure you provide an appropriate translation.
9. Generate electronic submissions in accordance with regulatory requirements.
10. Once you have prepared your regulatory submission, examine it thoroughly to ensure it is accurate and complete (e.g., no missing pages within a hard copy, no broken links within an electronic submission) before you submit it to the regulatory agency
11. There have been many advances in manufacturing science and in our understanding of quality systems. In addition, many pharmaceutical manufacturers are already implementing comprehensive, modern quality systems and risk management approaches.

Aim and objectives

- To provide the information and data needed by a regulatory agency to establish whether a regulated healthcare product can progress to clinical testing or whether it is safe and effective for marketing.
- To prepare this guidence by the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER).
- For additional information on how FDA interprets and intends to implement the electronic submission requirements of section 745A (a) of the FD&C Act.
- The Regulatory Affairs departments of life-science companies ensure that their companies comply with all of the regulations and laws concerning their business.

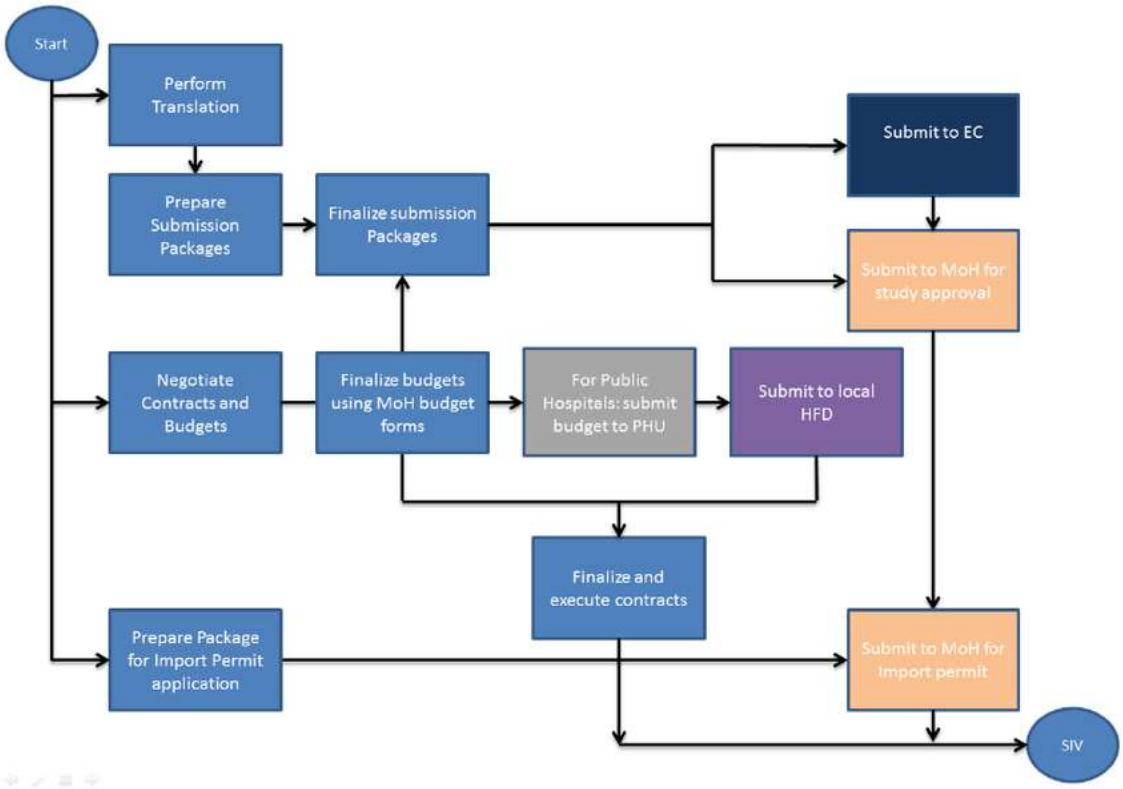

Fig 1 : Schematic Summary of Regulatory Submissions

The CGMP

CGMP refers to the Current Good Manufacturing Practice regulations enforced by the FDA. CGMPs provide for systems that assure proper design, monitoring, and control of manufacturing processes and facilities. Adherence to the CGMP regulations assures the identity, strength, quality, and purity of drug products by requiring that manufacturers of medications adequately control manufacturing operations. This includes establishing strong quality management systems, obtaining appropriate quality raw materials, establishing robust operating procedures, detecting and investigating product quality deviations, and maintaining reliable testing laboratories. This formal system of controls at a pharmaceutical company, if adequately put into practice, helps to prevent instances of contamination, mix-ups, deviations, failures, and errors. This assures that drug products meet their quality standards.

The CGMP requirements were established to be flexible in order to allow each manufacturer to decide individually how to best implement the necessary controls by using scientifically sound design, processing methods, and testing procedures. The flexibility in these regulations allows companies to use modern technologies and innovative approaches to achieve higher quality through continual improvement. Accordingly, the "C" in CGMP stands for "current," requiring companies to use technologies and systems that are up-to-date in order to comply with the regulations. Systems and equipment that may have been "top-of-the-line" to prevent contamination, mix-ups, and errors 10 or 20 years ago may be less than adequate by today's standards.

Fig 2: cGMP overview

Goal of the Guidance

This guidance describes a comprehensive quality systems model, which, if implemented, will allow manufacturers to support and sustain robust, modern quality systems that are consistent with CGMP regulations. The guidance demonstrates how and where the elements of this comprehensive model can fit within the requirements of the CGMP regulations. The inherent flexibility of the CGMP regulations should enable manufacturers to implement a quality system in a form that is appropriate for their specific operations
The overarching philosophy articulated in both the CGMP regulations *and* in robust modern quality systems is:

Quality should be built into the product, and testing alone cannot be relied on to ensure product quality

This guidance is intended to serve as a bridge between the 1978 regulations and our current understanding of quality systems. In addition to being part of the FDA's CGMP initiative, this guidance is being issued for a number of reasons:

1. A quality system addresses the public and private sectors' mutual goal of providing a high-quality drug product to patients and prescribers. A well-built quality system should reduce the number of (or prevent) recalls, returned or salvaged products, and defective products entering the marketplace.
2. It is important that the CGMP regulations are harmonized to the extent possible with other widely used quality management systems, including ISO 9000, non-U.S. pharmaceutical quality management requirements, and FDA's own medical device quality system regulations.
3. This guidance serves as a first step to highlight common elements between the CGMP regulations and Quality Management Systems. With the globalization of pharmaceutical manufacturing and the increasing prevalence of drug- and biologic-device combination products, the convergence of quality management principles across different regions and among various product types is very desirable.
4. The FDA has concluded that modern quality systems, when coupled with manufacturing process and product knowledge and the use of effective risk management practices, can handle many types of changes to facilities, equipment, and processes without the need for prior approval regulatory submissions. Manufacturers with a robust quality system and appropriate process knowledge can implement many types of improvements. In addition, an effective quality system, by lowering the risk of manufacturing problems, may result in shorter and fewer FDA inspections.
5. A quality system can provide the necessary framework for implementing *quality by design*4 (building in quality from the development phase and throughout a product's life cycle), continual improvement, and risk management in the drug manufacturing process. A quality system adopted by a manufacturer can be tailored to fit the specific environment, taking into account factors such as scope of operations, complexity of processes, and appropriate use of finite resources.

Under section 745A(a) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), at least 24 months after the issuance of a final guidance document in which the Food and Drug Administration (FDA) has specified the electronic format for submitting certain submission types to the Agency, such content must be submitted electronically and in the format specified by FDA**.** This guidance and the technical specifications documents it incorporates by reference describe the requirements for an electronic submission of standardized clinical and nonclinical study data under section 745A(a) of the FD&C Act. In accordance with section 745A(a), following the issuance of a final guidance on this topic, study data contained in the submission types identified in this guidance must be submitted electronically in a format that FDA can process, review, and archive.

This guidance implements the electronic submission requirements of section 745A(a) of the FD&C Act for study data contained in new drug applications (NDAs), abbreviated new drug applications (ANDAs),

biologics license applications (BLAs), and investigational new drug applications (INDs) to the Center for Drug Evaluation and Research (CDER) or the Center for Biologics Evaluation and Research (CBER) by specifying the format for electronic submissions. Submissions that are not submitted electronically and electronic submissions that are not in a format that FDA can process, review, and archive will not be filed or received, unless exempted from the electronic submission requirements (see section II.B).

In section 745A (a), Congress granted explicit authorization to FDA to implement the statutory electronic submission requirements in guidance. Accordingly, as indicated by the use of the words must or required, this document is not subject to the usual restrictions in FDA's good guidance practice (GGP) regulations, such as the requirement that guidances not establish legally enforceable responsibilities. See 21 CFR 10.115(d).[5]

The eCTD benefits health authorities (HAs) by allowing assessors to use computer-based tools such as searching, copying and pasting text, making the review process more efficient. The review of application dossier can be completed online, allowing for more timely reviews to meet legislative timelines, which ultimately benefits applicants, as well. For pharmaceutical companies, eCTD submissions can be less expensive to produce and ship.

Since the introduction the eCTD in FDA, submissions to FDA using the electronic format have continued to grow steadily. In FDA eCTD submission was about 9% of NDAs and 6% of INDs in 2007 and increased to around 73% and 58% of NDAs and INDs in 2011, respectively. In EMA the number of eCTD submissions spiked almost 50% in a six-month period spanning 2007 and 2008. The volume of eCTD submissions grew from 1,435 in the second half of 2007 to 2,122 by the end of the first half of 2008. In the future, the paper CTD is destined to be replaced by its electronic counterpart, the electronic Submission. In ICH regions eCTD format will be the only accepted electronic format by HAs.

FDA and other regulatory authorities use software to validate applicant's eCTD submission. Agencies have become more strict on the eCTD compliance with the validation criteria. In addition, the evolution of regulatory requirements (eCTD, electronic Application Form, Risk Management Plan, etc) is quite fast and often.[6]

Failure to pass the validation process will result in HAs refusing to receive the submission and the applicant will be asked to correct the errors and resubmit. Even a submission passes technical validation, during the management validation several medium severity errors combined with lack of navigation aids in the form of table of contents, bookmarks and hyperlinks could still lead to a "refuse to file".

In addition to these basic principles, each step can be optimized according to type of applications, or complexity of the submission, to adapt the business process to comply with regulatory submission regulation and to increase the efficiency in preparation and management of electronic submission.[7]

Introduction to the Regulatory Affairs in The Pharmaceutical Industry

The regulation of medical products has been expanding since early 20th century. Regulatory agencies are being established in an ever increasing number of countries across the globe. Regulatory affairs (RA) professionals are employed in pharmaceutical industry, government, academic research and clinical institutions**.** Pharma regulatory affairs professionals play an essential role in ensuring all pharmaceutical products comply with regulations governing the industry.

The RA professional is the primary link between the company and worldwide regulatory agencies such as US Food and Drug Administration (USFDA), Medicines and Healthcare Products Regulatory Agency, United Kingdom, (MHRA), Therapeutic Goods Administration,(TGA) Australia, European Medicines Agency (EMA), Organization of Economic Collaboration and Development (OECD) and Health Canada.

During 1950s, multiple tragedies i.e. sulfanilamide elixir, vaccine tragedy and thalidomide tragedy have resulted in substantial increase of legislations for drug products quality, safety and efficacy. This has also resulted into stricter norms for Marketing Authorization (MA) and Good Manufacturing Practices (GMPs).

Drug Regulatory Affairs is a dynamic, rewardingfield that embraces both scientific and legal aspects of drug development. DRA professionals are dedicated individuals who take pride in their contribution to improving the health and quality of life of peoples.

Importance of regulatory affairs

A new entity can cost several millions of rupees or dollars to progress. Surprisingly, even a few month deferrals in taking it to the market can have substantial impact on the monetary status of the company. One of the vital activities of the regulatory specialist is to ensure that the label of the product and related information of the patient has correctly been established and even a small mistake in any of the regulatory activities can make the product to be ready for recall in addition to the loss of several millions of money which is eventually bound to give rise to fall in self-assurance of financiers, health experts and finally the patients.

CONCLUSION

This guidance implements the electronic submission requirements of section 745A (a) of the FD&C Act for the electronic format of the content submitted in new drug applications (NDAs), abbreviated new drug applications (ANDAs), certain biologics license applications (BLAs), and certain investigational new drug applications (INDs) to the Center for Drug Evaluation and Research (CDER) or the Center for Biologics Evaluation and Research (CBER). See section III.A of this document for more information regarding required submission types. Submissions that are not submitted electronically and electronic submissions that are not in a format that FDA can process, review, and archive will not be filed or received, unless exempted from the electronic submission requirements. **T**his guidance and the technical specification documents it incorporates by reference describe how sponsors and applicants must organize the content that they submit to the Agency electronically for all submission types under section 745A(a) of the FD&C Act**.**

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