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Review

Inter Relationship Between Ra, QA, QC For Regulatory Submission

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Abstract

This guidance is intended to help manufacturers implementing modern quality systems and risk management approaches to meet the requirements of the Agency's current good manufacturing practice (CGMP) regulations (2l CFR parts 210 and 211). Many of the modern quality system concepts described here correlate very closely with the CGMP regulations. Current industry practice generally divides the responsibilities of the quality control unit (QCU), as defined in the CGMP regulations, between quality control (QC) and quality assurance (QA) functions. QC usually involves (1) assessing the suitability of incoming components, containers, closures, labeling, in-process materials, and the finished products; (2) evaluating the performance of the manufacturing process to ensure adherence to proper specifications and limits; and (3) determining the acceptability of each batch for release. QA primarily involves (1) review and approval of all procedures related to production and maintenance, (2) review of associated records, and (3) auditing and performing/evaluating trend analyses. The concept of a *quality unit* is also consistent with modern quality systems in ensuring that the various operations associated with all systems are appropriately planned, approved, conducted, and monitored. *Quality by design* means designing and developing a product and associated manufacturing processes that will be used during product development to ensure that the product consistently attains a predefined quality at the end of the manufacturing process. Quality by design, in conjunction with a quality system, provides a sound framework for the transfer of product knowledge and process understanding from drug development to the commercial manufacturing processes and for post-development changes and optimization.

Keywords: Ra, QA, QC

INTRODUCTION

Regulatory submission or documentation

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

Types of regulatory submissions:

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. 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.

The CGMPs for the 21st Century Initiative steering committee created a Quality System Guidance Development working group (QS working group) to compare the current CGMP regulations, which call for some specific quality management elements, to other existing quality management systems. The QS working group

mapped the relationship between CGMP regulations (parts 210 and 211 and the 1978 Preamble to the CGMP regulations2) and various quality system models, such as the Drug Manufacturing Inspections Program (i.e., systems-based inspectional program),3 the Environmental Protection Agency's Guidance for Developing Quality Systems for Environmental Programs, ISO Quality Standards, other quality publications, and experience from regulatory cases. The QS working group determined that, although the CGMP regulations do provide great flexibility, they do not incorporate explicitly all of the elements that today constitute most quality management systems. The CGMP regulations and other quality management systems differ somewhat in organization and in certain constituent elements; however, they are very similar and share underlying principles. For example, the CGMP regulations stress quality control. More recently developed quality systems stress quality management, quality assurance, and the use of risk management tools, in addition to quality control. The QS working group decided that it would be very useful to examine exactly how the CGMP regulations and the elements of a modern, comprehensive quality system fit together in today's manufacturing world. This guidance is the result of that examination.

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.

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.

The regulatory professional Responsibilities

1. The regulatory professional's job is to keep track of the ever-changing legislation in all the regions in which the company wishes to distribute its products.
2. They also advise on the legal and scientific restraints and requirements, and collect, collate and evaluate the scientific data their research and development colleagues are generating. They are responsible for the presentation of registration documents to regulatory agencies, and carry out all the subsequent negotiations necessary to obtain and maintain marketing authorization for the products concerned.
3. They give strategic and technical advice at the highest level in their companies, right from the beginning of the development of a product, making an important contribution both commercially and scientifically to the success of a development program and the company as a whole.
4. Preparation of organized and scientifically valid NDA(New drug application), ANDA(Abbreviated New Drug Application), INDA(Investigational New Drug Application), MAA(*Marketing Authorization Application),* DMF(Drug Master File) submissions.
5. Ensure adherence and compliance with all the applicable cGMP(Good Manufacturing Practices), ICH(*International Conference on Harmonization), GCP*(Good Clinical Practices), GLP(Good Laboratory Practices) guidelines, regulations and laws
6. Providing expertise and regulatory intelligence in translating regulatory requirements into practical workable plans
7. Advising the companies on regulatory aspects and climate that would affect their proposed activities
8. Apart from the above main roles, there are various other roles which Regulatory Affairs professionals play.

Regulatory societies

- The Regulatory Affairs Professionals Society (RAPS)
- The Organization for Professionals in Regulatory Affairs(TOPRA)
- The Canadian Association of Professional Regulatory Affairs (CAPRA)

The Regulatory Affairs Professionals Society (RAPS)

The Regulatory Affairs Professionals Society (RAPS) is the largest global organization of and for those involved with the regulation of healthcare and related products, including medical devices, pharmaceuticals, biologics and nutritional products. Founded in 1976, RAPS helped establish the regulatory profession and continues to actively support the professional and lead the profession as a neutral, non-lobbying nonprofit organization.

Quality assurance

Principle

QA is a wide-ranging concept covering all matters that individually or collectively influence the quality of a product. It is the totality of the arrangements made with the object of ensuring that pharmaceutical products are of the quality required for their intended use. QA, therefore, incorporates GMP and other factors, including those outside the scope of this guide such as product design and development.

The system of QA appropriate to the manufacture of pharmaceutical products should ensure that

Pharmaceutical products are designed and developed in a way that takes account of the requirements of GMP and other associated codes such.

Good manufacturing practices for pharmaceutical products, Part One. In: WHO Expert Committeeon Specifications for Pharmaceutical Preparations. Thirty-second report. Geneva, WorldHealth Organization, 1992, Annex 1 (WHO Technical Report Series, No. 823); and in: Qualityassurance of pharmaceuticals. Acompendium of guidelines and related materials. Volume 2,Second updated edition. Good manufacturing practices and inspection. Geneva, World HealthOrganization, 2007; and in: Quality assurance of pharmaceuticals. A

compendium of guidelinesand related materials. Geneva, World Health Organization, 2010 (CD-ROM).104as those of good laboratory practice (GLP) 737 and good clinical practice (GCP)

Good Manufacturing Practices

Good Manufacturing Practices (GMP) constitute an international set of guidelines for the manufacture of drugs and medical devices in order to ensure the production of quality products. In recent years, GMP protocols are being adopted and followed in over 100 countries, either in the form of regulations (Japan, Korea and United States), or Directives (European Union) or Guides (United Kingdom) or Codes (Australia). The objective of GMPs is to minimize risks with reference to the manufacturing, packaging, testing, labeling, distributing and importing of drugs, cosmetics, medical devices, blood and blood products, food items etc. These protocols are largely concerned with parameters such as drug quality, safety, efficacy and potency.

WHO GMP Protocols

World Health Organization GMP guidelines were instituted in 1975 in order to assist regulatory authorities in different countries to ensure consistency in quality, safety and efficacy standards while importing and exporting drugs and related products. India is one of the signatories to the certification scheme. The WHO-GMP certification, which possesses two-year validity, may be granted both by CDSCO and state regulatory authorities after a thorough inspection of the manufacturing premises.

Schedule M Compliance

The requirements specified under the upgraded Schedule 'M' for GMP have become mandatory for pharmaceutical units in India w.e.f. July 1, 2005. Schedule M classifies the various statutory requirements mandatory for drugs, medical devices and other categories of products as per the current Good Manufacturing Practices (cGMP). Schedule M protocols have been revised to harmonize it along the lines of WHO and US-FDA protocols. These revised protocols include detailed specifications on infrastructure and premises, environmental safety and health measures, production and operation controls, quality control and assurance and stability and validation studies.ii Problems related to Schedule M compliance are mostly confined to small-scale pharmaceutical units as large-scale firms have shown greater willingness to comply with the revised norms in order to increase their competitiveness in the global arena. The Central Drugs Standards Control Organization has, however, yet to compile data on the extent of Schedule M compliance by the firms. The Najma Heptullah Committee on Subordinate Legislation, which tabled its report in Parliament recently, is scheduled to compile data on extent of Schedule M compliance shortly. However, according to state regulatory sources, units in states like Gujarat, Karnataka, Maharashtra and Andhra Pradesh have achieved a high percentage of Schedule M compliance in comparison to units in other states.

The scope of regulatory intelligence(RI) encompasses multiple sources; monitoring the regulatory landscape/environment; RI-Databases; and other regulatory sources to research questions on regulatory issues such as analysing, discussing of possible procedure types as well as its implementation in compliance with agency's requirements inclusively awareness of advantages/ disadvantages of each single choice of procedure type selected. The regulatory world is a living and evolving body. Therefore, it is crucial to understand the necessity of monitoring the regulatory environment and agencies' requirements as result of this evolutionary process. RI provides the Regulatory Professional with Information to identify opportunities such as broader indications; roadmap to product approval; identify possible hurdles e.g. compliance issues; change in requirements for certain indication. In addition, RI helps Regulatory Professionals to predict Agency approval requirements as well as its review times. The consequence of monitoring and gathering of RI will be finally the development of a regulatory strategy which leads to generate valuable advantages such as decrease in approval time, reduce of costs of drug development based on current information as well as maximizing of the target market(s).

Definition of Regulatory Intelligence (RI)

Regarding to the different languages in the European Union and EEA, the word 'intelligence' may vary in its interpretation within the European countries. There are different definitions for 'regulatory intelligence' (RI). However, relying upon the English language and in accordance with the standard dictionary "Oxford English Dictionary" can give a further definition for RI.

However, two Regulatory Intelligence Network Groups (RINGs) in association with the Drug Information Association (DIA) have proposed the following definition:

RI is defined as "the act of gathering and analyzing publicly available regulatory information. This includes communicating the implications of that information, and monitoring the current regulatory environment for opportunities to shape future regulations, guidance, policy, and legislation" (Regulatory Intelligence Working Group, Regulatory Intelligence, 2010). The scope of regulatory intelligence encompasses multiple sources; monitoring the regulatory landscape/environment; RI-Databases; and other regulatory sources to research questions on regulatory issues such as analysing, discussing of possible procedure choices as well as its

implementation in compliance with agency's requirements inclusively the advantages/ disadvantages of each single choice. The Methodology applied in this includes two kinds of research online research and internal research.

Online Research

Research and/or Monitoring

1. Primary Research in e.g. pharmaceutical industry, regulatory affairs, business development, Licensing and R&D, government health ministries and regulatory agencies, as well as other relevant regulatory sources such as groups and associations, etc.
2. Secondary Research such as patent searching, trade journals, annual reports and other company's literature, published regulatory agency materials, etc.

Internal research

Qualitative Research

1. Preparation of department specific questions and common questions as well- regarding to- not only gathering information on competitor companies- but also tracking and update of these as well as its communication within the company
2. Performance of interviews with employees of different disciplines
3. Carrying out analyzes of the interview research results

Current discussions on ways how to optimize the drug regulatory system frequently address the need to apply the "risk based approach". But the meaning of the phrase is unclear, and so is the estimation of the value of this tool: Is it just another buzzword, or is it a valuable tool with broad applicability. Historically managing risk to health has always been in the focus of drug regulations: Issues of adulterated drugs potentially posing economic and health risks to consumers triggered the public interest in food and drug regulation in US resulting in the original food and drug act in 19061. The thalidomide disaster massively influenced the European drug regulations, and triggered the introduction of Directive 65/65/EEC (on the approximation of provisions laid down by law, regulation and administrative action relating to medicinal products) in 1965 (Rägo 2008).

Regulatory Issues in the Indian PharmaceuticalIndustry

The principal regulatory bodies entrusted with the responsibility of ensuring the approval, production and marketing of quality drugs in India at reasonable prices are:

CDSCO

The **Central Drug Standards and Control Organization (CDSCO),** located under the aegis of the Ministry of Health and Family Welfare. The CDSCO prescribes standards and measures for ensuring the safety, efficacy and quality of drugs, cosmetics, diagnostics and devices in the country; regulates the market authorization of new drugs and clinical trials standards; supervises drug imports and approves licenses to manufacture the above-mentioned products;

The **National Pharmaceutical Pricing Authority (NPPA),** which was instituted in 1997 under the Department of Chemicals and Petrochemicals, which fixes or revises the prices of decontrolled bulk drugs and formulations at judicious intervals; periodically updates the list under price control through inclusion and exclusion of drugs in accordance with established guidelines; maintains data on production, exports and imports and market share of pharmaceutical firms; and enforces and monitors the availability of medicines in addition to imparting inputs to Parliament in issues pertaining to drug pricing

In India, drug manufacturing, quality and marketing is regulated in accordance with the Drugs and Cosmetics Act of 1940 and Rules 1945. This act has witnessed several amendments over the last few decades. The Drugs Controller General of India (DCGI), who heads the Central Drugs Standards Control Organization (CDSCO), assumes responsibility for the amendments to the Acts and Rules. Other major related Acts and Rules include the Pharmacy Act of 1948, The Drugs and Magic Remedies Act of 1954 and Drug Prices Control Order (DPCO) 1995.

Some of the important schedules of the Drugs and Cosmetic Act includedealing with Schedule M: which, deals with Good Manufacturing Practices involving premises and plants and Schedule Y: which specifies guidelines for clinical trials, import and manufacture of new drugs. In accordance with the Act of 1940, there exists a system of dual regulatory control or control at both Central and State government levels. The central regulatory authority undertakes approval of new drugs, clinical trials, standards setting, control over imported drugs and coordination of state bodies' activities. State authorities assume responsibility for issuing licenses and monitoring manufacture, distribution and sale of drugs and other related products.

The agreement to assemble all the Quality, Safety and Efficacy information in a common format (called CTD - Common Technical Document) has revolutionised the regulatory review processes, led to harmonised

electronic submission that, in turn, enabled implementation of good review practices. For industries, it has eliminated the need to reformat the information for submission to the different ICH regulatory authorities.
The CTD is organised into five modules. Module 1 is region specific and Modules 2, 3, 4 and 5 are intended to be common for all regions. In July 2003, the CTD became the mandatory format for new drug applications in the EU and Japan, and the strongly recommended format of choice for NDAs submitted to the FDA.

M4 (R3): Organisation Including the Granularity document that provides guidance on document location and paginations.
The overall organisation of the CTD is presented here.
The CTD is organised into five modules:
Module1 is for administrative information and prescribing information, and should contain documents that are specific to each region; for example, application forms or the proposed label for use in the region. Module 2 contains the CTD summaries and should begin with a general introduction to the drug, including its pharmacological class, mode of action and proposed clinical use. Module 2 should also provide the overall summary of the 'quality' information provided, the non-clinical overview and the clinical overview, as well as the non-clinical written summaries and the tabulated summaries, and the clinical summary. As a foundation for the aforementioned material, module 3 contains information on quality topics, module 4 contains the nonclinical study reports and module 5 contains the clinical study reports.

M4 Q&As Document (R3)
In order to help users deal with issues which may arise during attempts to use the CTD, the ICH has supplied a Questions & Answers section on the ICH web site to answer most, if not all, questions anyone may have. If issues arise that are not answered on the web site, additional questions can be submitted for a formal response.

M4 Q (R1) Quality
Module 2: Quality Overall Summary (QOS)
Module 3: Quality
The section of the application covering chemical and pharmaceutical data including data for biological/ biotechnological products.
Re-edited with Numbering and Section Headers changes, September 2002
The Quality section of the Common Technical Document (M4Q) provides a harmonised structure and format for presenting CMC (Chemistry, Manufacturing and Controls) information in a registration dossier. The table of contents includes sections on Drug Substance and Drug Product. There are also sections for regional specific information as well as some appendices. Due to the fact that many CMC topics have not yet been the subject of ICH guidelines (e.g. drug substance synthesis, drug product manufacture, container closure), the content of M4Q is not totally harmonised. A new section on Pharmaceutical Development has been included to replace the Development Pharmaceutics Report (currently a part of the EU submission requirements). Also, a new CMC summary document, the Quality Overall Summary, has been developed.

M4S (R2)
Nonclinical Summaries and Organisation of Module 4
The non-clinical section of the application.
Re-edited with Numbering and Section Headers changes, September 2002
The CTD Safety (M4S) Guideline delineates the structure and format of the nonclinical summaries in Module 2 of the Common Technical Document, and provides the organisation of Module 4, the Nonclinical Study Reports. The Nonclinical Overview should present an integrated and critical assessment of the pharmacologic, pharmacokinetic, and toxicologic evaluation of the pharmaceutical, and generally should not exceed 30 pages. The Nonclinical Written Summaries (100 - 150 pages) are recommended to provide more extensive summaries and discussion of the nonclinical information on pharmacology, pharmacokinetics and toxicology. Thirty-four templates are provided for the preparation of the Nonclincal Tabulated Summaries, and 31 example tables are provided. Finally, the organisation of the Nonclinical Study Reports in Module 4 is described. Preparation of the nonclinical sections of the Common Technical Document according to the M4S Guideline results in a single harmonised dossier of the nonclinical information that is acceptable in all three ICH regions.

M4E (R1)
Module 2: Clinical Overview and Clinical Summary
Module 5: Clinical Study Reports
The clinical section of the Application.
Re-edited with Numbering and Section Headers changes, September 2002. CTD-Efficacy (M4E) describes the structure and format of the clinical data in an application, including summaries and detailed study

reports. There are two high level clinical summaries in Module 2 of the CTD : the Clinical Overview, a short document that provides a critical assessment of the clinical data; and the Clinical Summary, a longer document that focuses on data summarisation and integration. Clinical Study Reports and raw data (where applicable) are included in Module 5 of the CTD.

M4E (R2)

Description: Revision of M4E Guideline on Enhancing the Format and Structure of Benefit-Risk Information in ICH. This topic was endorsed by the ICH Steering Committee in April 2015.

The M4E(R2) Concept Paper proposed a review and revision in some parts of the Section 2.5 Clinical Overview of the Module 2 of the Common Technical Document (CTD) (Section 2.5.1 and 2.5.6) to ensure the guideline is both harmonised and sensible in its entirety.

The Common Technical Document (CTD) is a set of specification for application dossier for the registration of Medicines and designed to be used across Europe, Japan and the United States. It is an internationally agreed format for the preparation of applications regarding new drugs intended to be submitted to regional regulatory authorities in participating countries. It was developed by the European Medicines Agency (EMA, Europe), the Food and Drug Administration (FDA, US) and the Ministry of Health, Labour and Welfare (Japan). The CTD is maintained by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)

The Common Technical Document is divided into five modules:

1. Administrative and prescribing information
2. Overview and summary of modules 3 to 5
3. Quality (pharmaceutical documentation)
4. Preclinical (Pharmacology/Toxicology)
5. Clinical – efficacy (Clinical Trials)

Detailed subheadings for each Module are specified for all jurisdictions. The contents of Module 1 and certain subheadings of other Modules will differ, based on national requirements.

After the United States, European Union and Japan, the CTD has been adopted by several other countries including Canada and Switzerland.

The Electronic Common Technical Document (eCTD) is an interface for the pharmaceutical industry to agency transfer of regulatory information. The content is based on the Common Technical Document (CTD) format. It was developed by the International Conference on Harmonisation (ICH) Multidisciplinary Group 2 Expert Working Group (ICH M2 EWG). As of January 1, 2008, the U.S. Food and Drug Administration announced that the eCTD is the preferred format for electronic submissions.[1] To date, over 98,000 eCTD sequences have been submitted to the FDA.[2] Although the agency has not released an expected target date, the FDA revealed during the 2009 DIA Annual Meeting that it is looking at draft legislation to require eCTD.

eCTD (data structure)

The eCTD is a message specification for the transfer of files and metadata from a submitter to a receiver. The primary technical components are:

- A high level folder structure (reqed)
- An XML "backbone" file which provides metadata about content files and lifecycle instructions for the receiving system
- An optional lower level folder structure (recommended folder names are provided in Appendix 4 of the eCTD specification)
- Associated document type definitions (DTDs) and stylesheets.

Each submission message constitutes one "sequence". A cumulative eCTD consists of one or more sequences. While a single sequence may be viewed with web browser and the ICH stylesheet provided, viewing a cumulative eCTD requires specialized eCTD viewers.

The top part of the directory structure is as follows

In the 1980s, what is today the European Union began harmonising regulatory requirements. In 1989, Europe, Japan, and the United States began creating plans for harmonisation; ICH was created in April 1990 at a meeting in Brussels. The ICH has four major parts:

1. ICH Steering Committee
2. ICH Coordinators
3. ICH Secretariat
4. ICH Working Groups

The Steering Committee, made of six ICH Parties, governs the ICH, determining the policies and procedures, selecting topics for harmonisation and monitoring progress of harmonisation initiatives. The ICH consists of:

The ICH Coordinators represents each ICH Party to the ICH Secretariat on a day-to-day basis.

The ICH Secretariat is primarily concerned with preparations for, and documentation of, meetings of the Steering Committee as well as coordination of preparations for Working Group (EWG, IWG, Informal WG) and Discussion Group meetings.
The ICH Working Groups are created by the Steering Committee when a new topic is accepted for harmonisation, and is charged with developing a harmonised guideline that meets the objectives outlined in the Concept Paper and Business Plan.
Face-to-face meetings of the EWG will normally only take place during the biannual SC meetings. Interim reports are made at each meeting of the SC. If consensus is reached the EWG will sign the Step 2 Experts Signoff sheet and submit it to the SC to request adoption. If there is no agreement in the EWG within the time frame the SC may extend the time frame, suspend or abandon the harmonization project.

Step 2: Confirmation of EWG consensus by the SC
Step 2 is reached when the SC agrees, based on the report of the EWG, that there is sufficient scientific consensus on the technical issues for the draft guideline. This text is signed off by the SC as Step 2 Final Document.

Step 3: Regulatory consultation and discussion
The draft becomes subject of consultation in the three regions. It is published in the European Union (as draft CHMP or CVMP guideline), Japan (after translation by MHLW), and the USA (as draft guideline in the Federal Register) and everybody within these regions can comment on it. There is also an opportunity for companies, associations and authorities in non-ICH regions to comment on the draft, which is distributed by IFPMA and WHO. After obtaining all consultation results, the EWG will be resumed. A new rapporteur will be appointed from the regulatory party, preferably from the same region as the previous rapporteur. The same procedure described in Step 1 is used to address the consultation results into the Step 2 Final Document. The draft document to be generated as a result of the Step 3 phase is called Step 4 Experts Document. If industry and regulatory EWG members agree on the alterations as a result of the consultation, the Step 4 Experts Document is signed by the EWG regulatory experts only (Step 4 Experts Signoff) and submitted to the SC to request adoption as Step 4 of the ICH process..

Step 4: Adoption of an ICH harmonised tripartite guideline
Step 4 is reached when the SC agrees that there is sufficient scientific consensus on the technical issues. If one industry party has strong objections to the adoption of the guideline due to deviations of the revised draft from the original consensus the regulatory parties may agree that a revised document should be submitted for further consultation. In this case, the EWG discussion may be resumed.
The Step 4 Final Document is signed off by the SC signatories for the regulatory parties of ICH as an ICH Harmonized Tripartite Guideline.

Step 5: Implementation
The ICH Harmonized Tripartite Guideline moves immediately to the final step of the process that is the regulatory implementation. This step is carried out according to the same national/regional procedures that apply to other regional regulatory guidelines and requirements, in the European Union, Japan, and the United States.
Although adherence to overall CTD structure is necessary, it should be noted that no guideline can cover all eventualities, and common sense and a clear focus on the needs of the regulatory authority assessor are the best guides to constructing an acceptable document. Therefore, applicants can modify the format at some of the subsection levels, if needed to provide the best possible presentation of the information, in order to facilitate the understanding and evaluation.
This CTD guidance document is not applicable for the manufacture and sale of bulk drugs of a new drug approved in the country. In case of a new chemical entity, the approval of only API cannot be considered unless safety and efficacy of the finished formulation of the drug is evaluated and approved by this office.

Guidelines for preparation of CTD
CTD: overview
The CTD is organized into five modules (Module 1, 2, 3, 4, and 5) and a diagrammatic representation of organization of the CTD

Module 1: General Information
This module should contain documents specific to India; for example, Form 44, Treasury challan fee or the proposed label for use in India.

Module 2: CTD Summaries

This module should begin with a general introduction to the pharmaceutical, including its pharmacologic class, mode of action, and proposed clinical use, not exceeding one page. Module 2 should contain 7 sections in the following order:

- CTD table of contents
- CTD introduction
- Quality overall summary
- Nonclinical overview
- Clinical overview
- Nonclinical written and tabulated summaries
- Clinical summary

Module 3: Quality
Information on Quality should be presented in the structured format as described in Section 3.

Module 4: Nonclinical Study Reports
The nonclinical study reports should be presented in the order described at Section 4.
Module 5: Clinical Study Reports
The human study reports and related information should be presented in the order described at Section 5.

DISCUSSIONS

Quality Assurance
Quality assurance is a wide ranging concept covering all matters that individually or collectively influence the quality of a product. It is the totality of the arrangements made with the object of ensuring that pharmaceutical products are of the quality required for their intended use.

QA is the **heart and soul** of quality control
QA = QC + GMP

The System of Quality Assurance

- Pharmaceutical products are designed and developed in a way that takes account of the requirements of GMP and other associated codes such as those of good laboratory practice (GLP) and good clinical practice (GCP)
- Product and control operations are clearly specified in a written form and GMP requirements are adopted
- Managerial responsibilities are clearly specified in job description
- Arrangements are made for the manufacture, supply and use of the correct starting and packaging materials.
- All necessary controls on starting materials, intermediate products, and bulk products and other in-process controls, calibrations, and validations are carried out.
- The finished products is correctly processed and checked according to the defined procedures.
- Pharmaceutical products are not sold or supplied before the authorized persons have certified that each production batch has been produced and controlled in accordance with the requirements of the marketing authorization and any other regulations relevant to the production, control and release of pharmaceutical products
- Satisfactory arrangements exist to ensure, as far as possible, that the pharmaceutical products are stored by the manufacturer, distributed and subsequently handled so that quality is maintained throughout their shelf-life.
- There is a procedure for self-inspection and/or quality audit that regularly appraises the effectiveness and applicability of the quality assurance system
- Deviation are reported, investigated and recorded
- There is a system for approving changes that may have an impact on product quality
- Regular evaluations of the quality of pharmaceutical products should be conducted with the objective of verifying the consistency of the process and ensuring its continuous improvement.

CONCLUSION

Implementation of a comprehensive quality systems model for human and veterinary pharmaceutical products, including biological products, will facilitate compliance with 21 CFR parts 210 and 211. The central goal of a quality system is the consistent production of safe and effective products and ensuring that these activities are sustainable. Quality professionals are aware that good intentions alone will not ensure good products. A robust

quality system will promote process consistency by integrating effective knowledge-building mechanisms into daily operational decisions. Specifically, successful quality systems share the following characteristics, each of which has been discussed in detail above:

Science-based approaches

1. Decisions based on an understanding of the intended use of a product
2. Proper identification and control of areas of potential process weakness
3. Responsive deviation and investigation systems that lead to timely remediation
4. Sound methods for assessing and reducing risk
5. Well-defined processes and products, starting from development and extending throughout the product life cycle
6. Systems for careful analysis of product quality
7. Supportive management (philosophically and financially)

Both good manufacturing practice and good business practice require a robust quality system. When fully developed and effectively managed, a quality system will lead to consistent, predictable processes that ensure that pharmaceuticals are safe, effective, and available for the consumer.

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