



Introduction to CMC Regulatory Affairs

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My Background...

- **Experience**
 - ~4 years as CMC regulatory consultant
 - Currently working at SynerG Pharma Consulting, LLC Southborough, MA
 - Post approval & pre approval CMC submissions (both US and Global)
 - Small and large molecules
- **Education**
 - Bachelors in Pharmacy, Jawaharlal Nehru Technological University, India
 - MS in Regulatory Affairs of Drugs, Biologics and Medical Devices, Northeastern University, Boston, MA



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Syner-G Pharma Consulting, LLC (Syner-G)

- Provides full spectrum of customized CMC development solutions for Biopharmaceutical companies
- 20-30 employees
- Services: “CMC-360”
 - Technical development
 - CMC regulatory
 - Quality Assurance
 - Regulatory Intelligence
 - Ad-hoc Regulatory Operations



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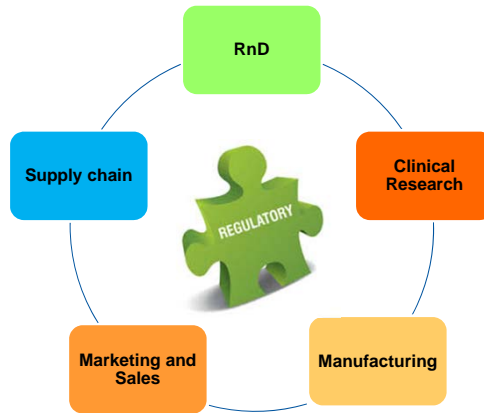
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Introduction to CMC regulatory Affairs

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What is Regulatory Affairs?

“Heart” of the pharmaceutical Industry



What is Regulatory Affairs? Contd..

- Critical role in converting a “molecule” with potential medicinal properties to “commercial medical product”



- Understand and Interpret Regulations and guidance from health authorities
 - Local vs Global
 - Determine requirements from the regulations
- Liaise between Biopharma and Health Authorities
 - Responsible for authoring Regulatory dossiers
 - Other communications
 - Meetings
- Various areas of regulatory include Clinical, CMC, labelling, Advertising and Promotion, Pharmacovigilance

CMC Regulatory Affairs (CMC-RA)

CMC stands for Chemistry, Manufacturing and Controls.

- **CMC RA group provides**
 - CMC regulatory leadership
 - Strategy
- **Ensures the medicinal product is**
 - Of Supreme Quality
 - Safe for the use in treatment of individuals
 - Manufactured per regulations
- **Interactions inside the company is with**
 - Technical operations or Manufacturing team
 - Quality Assurance
 - Analytical
 - Contract Manufacturing organizations
 - Supply chain
 - Labelling
- **Interactions with health authorities**
 - Authoring of regulatory dossiers
 - Briefing books
 - Any communication regarding quality of the product (eg: field alert reports, CPPs etc)
 - Maintenance of regulatory dossiers



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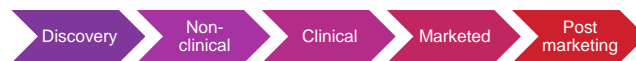
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Regulatory Dossiers and its contents

- **Some light on Pharma development:**
 - Timeline for development of a product takes 10-15 years
 - For a chemical/ biological entity to become a medicinal product includes various phases



- Regulatory approvals are required to conduct clinical studies and marketing the product.
- **Regulatory dossiers: Provide comprehensive information on**
 - Indication for use
 - Nonclinical data
 - Clinical data to support indication
 - Data to support the quality of the product
 - Label and storage conditions



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Regulatory Dossiers and its contents

Types of Regulatory dossiers:

- Pharmaceutical Regulatory dossiers are of 2 types
 - Clinical applications:
 - ✓ IND- Investigational New Drug Applications (in USA)or
 - ✓ CTA- Clinical trial application (Ex USA)
 - Market applications:
 - ✓ NDA- New Drug applications (FDA- for small molecules)
 - ✓ BLA- Biologic license Application (FDA- for Large molecules)
 - ✓ MAA- Market authorization application (Ex USA for both small and large molecules)



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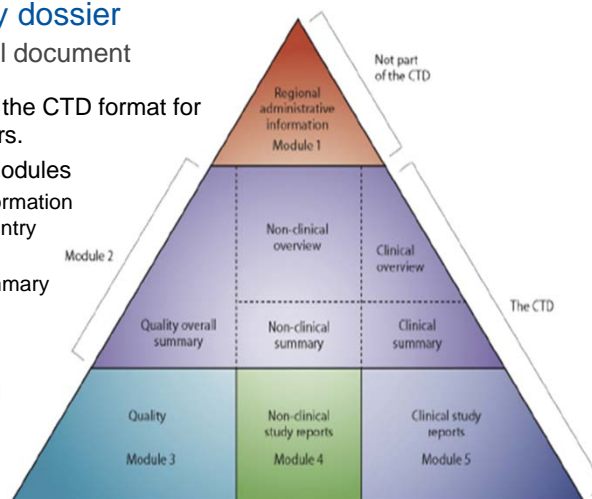
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Format of Regulatory dossier

CTD- Common Technical document

- ICH M4Q (R1) proposes the CTD format for all the regulatory dossiers.
- The CTD format has 5 modules
 - Module 1- Regional Information includes forms and country specific requirements
 - Module 2: provides summary for quality (CMC- 2.3), Efficacy (clinical) and Safety (non clinical)
 - Module 3, 4,5 :Detailed information on quality, safety and efficacy respectively



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CMC Modules of Regulatory Dossier

- Quality information is presented in Module 3 and Module 2.3
 - **Chemistry:**
 - Structure, synthesis the drug substance, the composition of drug product, the materials involved in it
 - **Manufacturing:**
 - Description of manufacture of the product, equipment used, Facility information
 - **Controls:**
 - Ensure the quality of the product
 - In-process controls
 - Specifications for testing drug substance and drug product
 - Stability of the product
- The detailed quality information presented in Module 3
- Summary of information in Module 3 is presented in Module 2.3 and is called as Quality Overall Summary (QOS)
- Module 3 is classified into 4 parts
 - 3.2.S- Drug Substance
 - 3.2.P- Drug Product
 - 3.2.A- Appendices
 - 3.2.R- Regional Information

Drug Substance- 3.2-S

S.1 General Information

- S.1.1- Nomenclature
- S.1.2- Structure
- S.1.3-General Properties

S.2- Manufacture

- S.2.1-Manufacture
- S.2.2- Description of Manufacturing process and Process controls
- S.2.3- Control of materials
- S.2.4-Critical Steps and Intermediates
- S.2.5- Process Validation
- S.2.6- Manufacturing Process Development

S.3- Characterization

- S.3.1- Elucidation of Structure
- S.3.2- impurities

Drug Substance- 3.2-S

S.4- Control of Drug Substance

- S.4.1- Specifications
- S.4.2- Analytical Methods
- S.4.3- validation of Analytical procedures
- S.4.4- Batch Analyses
- S.4.5- Justification of Specifications

S.5- Reference Standards

S.6- Container Closure System

S.7- Stability

- S.7.1- Stability Summary and Conclusion
- S.7.2- Stability Protocol
- S.7.3- Stability Data



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3.2.S- Drug Substance (DS)

- **Chemistry of the drug substance is described in S.1 and S.3 sections**
 - Nomenclature: Internal names, IUPAC, USAN, INN etc- S.1.1
 - Structure, stereochemistry, etc- S.1.2
 - Physical properties -S.1.3
 - Elucidation of Structure – S.3.1
 - Impurities of the drug substance- S.3.2
- **Synthesis of the drug substance is provided in S.2**
 - Manufacturers and their responsibilities are provided in S.2.1
 - Detailed Steps of DS synthesis, process flow is described in S.2.2
 - Materials that are used in the synthesis are discussed in S.2.3; Including
 - Starting materials,
 - Raw materials,
 - Reagents,
 - Residual solvents
 - Critical Steps in the process is discussed in S.2.4 which includes
 - Process design,
 - Process parameters
 - Validation of the process and supporting data is provided in S.2.5
 - The “story” behind how did we come up with the manufacturing process S.2.6
- **DS container closure in S.6:**
 - Dimensions and materials used
 - Any quality testing requirements for packaging



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Drug Product-3.2-P

P.1- Description and composition of drug product

P.2- Pharmaceutical Development

- P.2.1- Components of Drug product
 - P.2.1.1-Drug Substance
 - P.2.1.2-Excipients
- P.2.2- Drug product
 - P.2.2.1-Formulation Development
 - P.2.2.2-Overages
 - P.2.2.3-Physiochemical and Biological properties
- P.2.3-Manufacture and Process development
- P.2.4-Container closure system
- P.2.5-Microbial Attributes
- P.2.6-Compatibility

P.3-Manufacture

- P.3.1-Manufacturer
- P.3.2-Batch formula
- P.3.3.-Description of manufacturing process and process controls
- P.3.4-Control of Critical Steps and Intermediates
- P.3.5-Process Validation



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Drug Product-3.2-P

P.4-Control of Excipients

- P.4.1-Specifications
- P.4.2-Analytical Methods
- P.4.3-Validation of analytical methods
- P.4.4-Justification of Specifications
- P.4.5-Excipients of Human or Animal Origin
- P.4.6-Novel Excipients

P.5-Control of Drug Product

- P.5.1-Specifications
- P.5.2-Analytical Methods
- P.5.3-Validation of analytical methods
- P.5.4-Batch Analyses
- P.5.5-Characterization of Impurities
- P.5.6-Justification of Specification

P.6-Reference Standards or Materials

P.7-Container closure System

P.8-Stability

- P.8.1- Stability Summary and Conclusion
- P.8.2-Stability Protocol
- P.8.3-Stability Data



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3.2.P-Drug Product (DP)

- **Chemistry of the drug product is described in section P.1**
 - The description of the drug product: solid or liquid;
 - Dosage form: capsules or tablets; solution or suspension
 - The composition of the drug product is described in P.1 and P.2.1
 - Drug Substance
 - Excipients: Additive agents which bulk up and have certain function

- **The Pharmaceutical Development of the drug product is described in section P.2**
 - Section P.2.2 includes
 - Information on development of formulation
 - Formulation studies to come up with the formulation including any overages allowed
 - Properties of the drug product is presented in the section
 - Section P.2.3 includes
 - Detailed steps of Manufacturing,
 - Flowcharts
 - Process development
 - Process parameters including equipment
 - Section P.2.4 details the container closure system and DP compatibility it
 - The testing strategy for microbial attributes is presented in P.2.5
 - The compatibility of drug product is presented in P.2.6



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3.2.P-Drug Product (DP)

- **The manufacturing information for the drug product is described in P.3**
 - Similar to S.2.1, manufacturer including responsibilities of analytical testing, packaging, release and labelling of the product is outlined in P.3.1
 - Batch formula and scale of the batch is presented in P.3.2
 - The detailed in P.3.2 are about
 - Steps of manufacturing,
 - Manufacturing flowcharts,
 - Process parameters
 - Critical Steps in the process are discussed in P.3.4
 - Process design ,
 - Process parameters
 - Validation of the manufacturing process and supporting data is provided in section P.3.5

- **DP container closure in P.7:**
 - Dimensions
 - Materials used
 - Any quality testing requirements for packaging



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Control of Drug Substance and Drug Product

- **Certain sections like 3.2.S.4 and 3.2.P.5 outlines how does the sponsor makes sure that the quality of the product is intact- S.4 and P.5**
 - Specifications: Information on tests and acceptance criterion for quality testing for release and stability is presented in S.4.1 for DS and P.5.1 for DP
 - Analytical methods descriptions for the tests are presented in S.4.2 for DS and P.5.2 for DP
 - Validation procedure and data for the methods is presented in S.4.3 for DS and P.5.3 for DP
 - The batch release results based on the release specifications are presented in S.4.4 and P.5.4
 - The characterization of impurities of DP is presented in P.4.5
 - The justification for the specification is presented in S.4.5 and P.5.6

- **The control of excipients section P.4 outlines**
 - Specifications of the excipients in P.4.1
 - Analytical procedures for the tests for excipients in P.4.2
 - The validation data of the analytical procedures in P.4.3
 - Justification of Specifications in P.4.4
 - For excipients which are human and animal origin, information including the information on manufacturing and analytical information in P.4.5
 - Goes the same for new excipients in novel excipients section in P.4.6

Control of Drug Substance and Drug Product Contd..

- **Reference standard in Sections S.5 and P.6**
 - Is highly purified compound used as base for the measurement for batches
 - Information on reference standard presented in sections S. 5 and P.6 respectively includes
 - The lots for reference standard,
 - Specifications for reference standards

- **The stability of DS and DP is presented in S.7 and P.8**
 - The outlines the types of studies conducted and the summary of results in S.7.1 and P.8.1
 - The protocols for the stability studies including temperature conditions and studies that will be performed is outlined in S.7.2 and P.8.2. These also include any commitments like post approval studies are also provided in these sections
 - The detailed data results for the lots that have been tested per specifications and stability protocols is presented in S. 7.3 and P.8.3

3.2.A, 3.2.R and QOS

- The information on flow diagrams of the manufacturing areas if required will be presented in 3.2.A
- Any information specific to particular region is presented in 3.2.R
 - Eg: Comparability protocol or change management protocol
- **Quality Overall summary:**
 - The QOS is presented in Module 2 in section 2.3 also consists of 4 parts like Module 3
 - 2.3.S- Drug Substance
 - 2.3.P- Drug Product
 - 2.3.A- Appendices
 - 2.3.R- Regional Information
 - It is the concise version of Module 3 sections and provides good summary of the same

Guidance used to build Quality section

- ICH M4Q provides guidance on the format which is accepted in all the countries
- For the content of the Module 3
 - Country specific regulations
 - For eg: 21 CFR 314.50- Content and format of an application
 - Health Authority Guidance
 - Other ICH guidance like ICH Q1A-C, ICHQ3A-B, ICH Q6A-B, ICH 8, ICH Q9, ICH Q10, ICH Q11, ICH M7

Questions?

Please use the microphone indicated so our recording includes audio of your question

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For further information, please contact

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