신약개발에서 CMC의 역할

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What is CMC?

- **CMC: Chemistry, Manufacturing, and Controls**
- **What does CMC do?**

– To assure that the drug sold to the public will have quality attributes similar to those of the drug demonstrated to be safe and effective

– To assure that the quality of the drug meets appropriate standards and is consistent

– To assure that the drug you are using is the drug described on the label

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Kenakin, T. (2016). *Pharmacology in drug discovery and development: Understanding drug response*. Academic Press.

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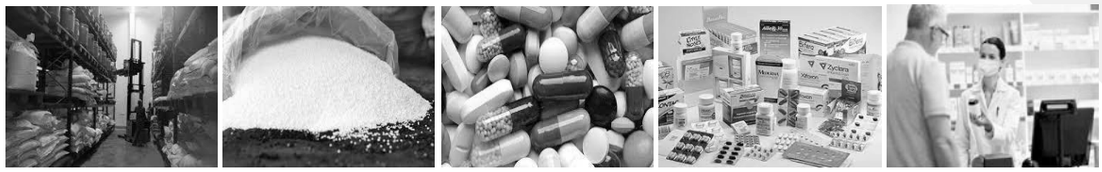
What is CMC?

Starting material → Drug substance/ API → Drug product → Packaging/ Label → Distribution to patient



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Requirements to Support IND

Requirements to Support IND

- IND Regulations and Guidance Documents
- CMC Information
- Review at IND and CMC Critical Elements
- CMC Information to Support IND

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—· IND Regulation & Guidance documentati

• Regulation

– 21 CFR 312.23(a)(7)(i)

• As appropriate for the particular investigations covered by the IND, a section describing the co… manufacture, and control of the drug substance and the drug product……

• ……. sufficient CMC information to assure the proper identification, quality, purity and strength … investigational drug, the amount of information needed will very with the phases….

• Guidance

- Content and Format of INDs for Phase 1 Studies of Drugs, Including Well
- Characterized, therapeutic Biotechnology
- Derived Products
- INDs for Phase 2 and Phase 3 Studies, chemistry, Manufacturing, and Controls Information
- cGMP for Phase 1 Investigational Drugs
- IND meetings for Human Drugs and Biologics
- Formal Meetings Between the FDA and Sponsors or Applicants
- ICH Q8, Q9, Q10

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—· CMC information

• CMC Information

– The graded nature of CMC information

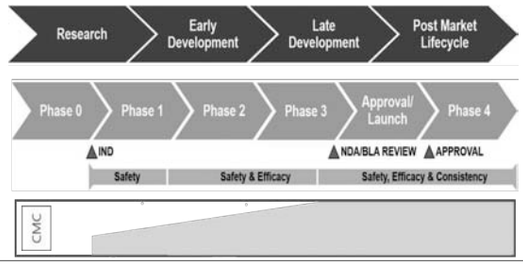
– The amount of CMC information needed varies according to type of trial

– phase, size and duration of clinical trial, dosage form, prior usage, history, etc.

– CMC development parallels clinical investigations

– Over time, change is inevitable; Product quality should be constant (or improve)!!

• Raw material suppliers, Manufacturing sites, Manufacturing processes, Manufacturing equipment, Packaging, Specifications, Testing procedures, etc.



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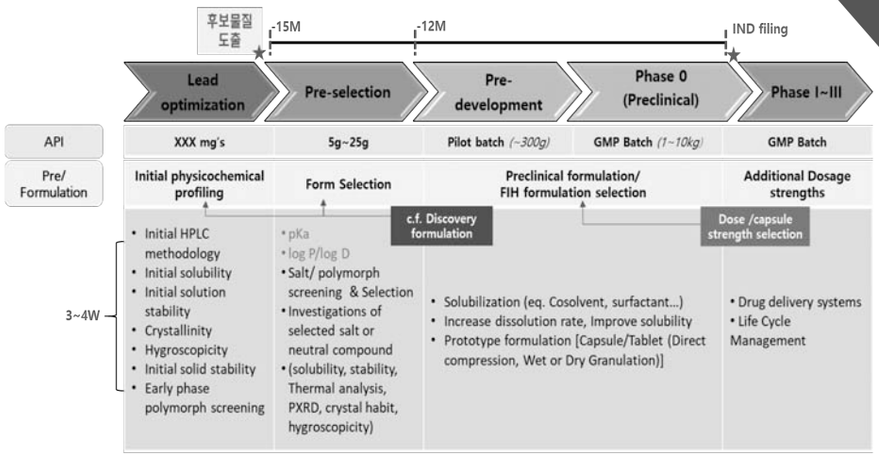
CMC information



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Review at IND and CMC Critical Elements

- To assure the safety of patients during all phases
  - Phase 1; Safety - the point of risk to patient
  - Phase 2 and Phase 3; Safety/efficacy and the linkage of the clinical test product to the to-be-marketed product
- Graded nature of CMC information from phase 1 to phase 3
  - Continue to provide CMC data to support clinical studies
  - Develop data for future NDA/BLA submission
- Demonstrate that the to-be-marketed drug has the same/similar identity, quality, purity and strength as that of the investigational drug product to be effective and sage through clinical studies
- Demonstrate consistency and reliability of drug manufacturing process over product life
- Systematic pharmaceutical development (ICH Q8, Q9, Q10)
- Make use of milestone meetings for early discussion of CMC or regulatory problems
- CMC Critical Elements
  - How and where is the drug made?
  - How are raw materials tested and monitored?
  - What control procedures are in place to assure product consistency and quality?
  - Are quality attributes adequately identified and characterized for the product?
  - Are the test methods used to monitor product quality appropriate?
  - How long does the product maintain its quality after it is made (shelf life/expiry)?

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CMC Information to Support IND - Drug Substance

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Drug Substance	Phase 1	Phase 2	Phase 3
Characterization and Description	• Brief description – physical, chemical, biological, etc. • Sufficient evidence to support chemical structure	• Safety updates on the information provided for Phase 1 • More detailed description of the configuration and chemical structure	• Complete description of the physical, chemical and biological characteristics and supporting evidence to elucidate and characterize the structure
Manufacturer	• Identified	• Addition, deletion or change of any manufacturer during Phase 1 • Contract laboratories for quality control and stability testing	
Synthesis/Method of Manufacture and controls	• Brief description of manufacturing process • List of reagents, solvents, catalysts, etc • Flow diagram – suggested	• Starting materials • Safety updates on reagents, solvents, auxiliary materials, proposed changes identified during earlier phases • Flow diagram • In-process controls • Reprocessing and pertinent controls – safety related	

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CMC Information to Support IND - Drug Substance

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Drug Substance	Phase 1	Phase 2	Phase 3
Reference standard	Recommended if available	Established	
Specification	• Proposed acceptance criteria supported by analytical data from clinical trial material • Brief description of analytical procedures • CoA - suggested	• Any change in the tentative specification from P1 • List of the test method • Test results, analytical data and CoA of clinical trial materials since original IND filing	• Impurities – identified, qualified and quantified as appropriate • Establish suitable limits based on manufacturing experience • Detailed list of tests • General description of the USP analytical procedures • Complete description of the non-USP analytical procedures with validation data

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CMC Information to Support IND - Drug Substance

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Drug Substance	Phase 1	Phase 2	Phase 3
Container/closure	Recommended if available	Brief information	Detailed information
Stability	• Brief description of stability study and analytical procedures • Preliminary stability data if available • Detailed stability data, stability protocol may not needed	• Stability indicating method • Stability protocol • Preliminary stability data on a representative material • All stability data for the clinical material used in P1	• Detailed stability protocol • Detailed stability data • Stress sturdies should be conducted

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CMC Information to Support IND - Drug Product

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Drug Substance	Phase 1	Phase 2	Phase 3
Components and composition	• List of all components • Quality of inactive ingredients (USP/NF) • Novel excipients – additional information • Brief summary of composition	• Any changes during earlier phase(s) • Established names and compendial status for components, if any • Quantitative composition per unit dose • Batch formula • List components used and removed during the manufacturing of the drug product for P2 • The formulations of certain drug product delivered by devices should be similar to that intended for the marketed drug product	
Stability	• Recommended	• Active – Any changes during earlier phase(s) • Compendial inactive – specify quality if changed • Noncompandial – analytical procedures and acceptance criteria for P2, full description of the characterization, manufacture, control, analytical procedures and acceptance criteria for P3	

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CMC Information to Support IND - Drug Product

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Drug Product	Phase 1	Phase 2	Phase 3
Components and composition	• List of all components • Quality of inactive ingredients (USP/NF) • Novel excipients – additional information • Brief summary of composition	• Any changes during earlier phase(s) • Established names and compendial status for components, if any • Quantitative composition per unit dose • Batch formula • List components used and removed during the manufacturing of the drug product for P2 • The formulations of certain drug product delivered by devices should be similar to that intended for the marketed drug product	
Stability	• Recommended	• Active – Any changes during earlier phase(s) • Compendial inactive – specify quality if changed • Noncompandial – analytical procedures and acceptance criteria for P2, full description of the characterization, manufacture, control, analytical procedures and acceptance criteria for P3	

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CMC Information to Support IND - Drug Product

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Drug Product	Phase 1	Phase 2	Phase 3
Manufacturer	Identified	Any changes during earlier phase(s) including contractor	
Method of manufacturing, packaging and process controls	• Brief description • Flow diagrams – suggested	• General step by step description for the unit dose • Flow diagram • Information on equipment, packaging and labeling process, in-process controls • Reprocessing procedures and controls • Brief description of the packaging and labeling for clinical supplies for P3	
Specification	• Proposed acceptance criteria supported by analytical data from clinical trial batch • Brief description of analytical procedures • CoA of the clinical batches – suggested	• Changes to specifications • Data updates on the degradation profile • Identification, qualification of degradation products for P3 • Batch analysis and CoA for the lots used in clinical studies	

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CMC Information to Support IND - Drug Product

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Drug Product	Phase 1	Phase 2	Phase 3
Container closure system	• Recommended	• Any changes during earlier phase(s) • Name of the manufacturer and supplier	
Stability	• Brief description of stability study and analytical procedures • Preliminary data	• Stability protocol • Preliminary (P2) and detailed (P3) stability data • All available stability data for the clinical material used in earlier phase(s) • Stress testing results for P3 • Container closure integrity tests for sterile products	

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Differences in Supporting a Small Molecules vs Biologics Development

Differences in Supporting a Small Molecules vs Biologics Development

- Definitions of Large Molecules

- Review at IND and CMC Critical Elements for Biologics

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Definitions of Large Molecules

• European Directive 2001/83/EC on Human Medicinal Products:

A biological medicinal product is a product, the active substance of which is a biological substance. A biological substance is a substance that is produced by or extracted from a biological source and that needs for its characterisation and the determination of its quality a combination of physicochemical-biological testing, together with the production

• US Public Health Service Act (Section 351):

The term "biological product" means a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein (except any chemically synthesized polypeptide), or analogous product…applicable to the prev ase or condition of human beings.

Large Molecules =

Antibody
Cell therapy
Vaccine
Biologics
Antibody – Drug Conjugate
Chemically modified protein

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Differences between Biologics and their Drugs

- Biologics are large, complex molecules and may be whole cells
- Biologics usually have complex, heterogeneous composition
  - Potentially numerous process- and product-related impurities
  - Change in the manufacturing process can cause change in product or impurity composition
- Exact structure may be unknown (e.g., all possible variants often not fully characterized) and can change with changes in culture conditions and during purification
  - Physical changes
    - Aggregation
    - Mis-folding
    - Truncation, proteolysis
- Chemical complexity
- Complex manufacturing process (living organism, cell banks)
  - Multiple types of active (drug) substance
  - Different starting points
  - Many unit operations with complex controls
- Immunogenicity (Safety/Efficacy) and comparability (Consistency)
- Same question: How does the manufacturer ensure the product is manufactured consistently?

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Review at IND and CMC Critical Elements for Biologics

- To assure the safety of patients during all phases
- Data/Information and the understanding of the products critical quality attributes and mechanism of the action
- Effective Communication with Health Authorities
- CMC Critical Information for Biologics
  - Expression System
  - Cell Banks
  - Manufacturing process
  - Release specifications
  - Stability data
  - Container closure system
  - Description of product
    - Mechanism of action if known
    - Characterization data
  - Immunogenicity

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CMC Information to Support NDA/BLA

- CMC Information to Support NDA/BLA
  - CMC Information Differences between INDs and NDAs
  - CTD Triangle and Module 3 – Quality
  - Module 3 – Quality – 3.2.S Drug Substance
  - Module 3 – Quality – 3.2.P Drug Product

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CMC Information Differences between INDs and NDAs

	INDs	NDAs
ICH Quality Guidelines	Do not apply	Apply
Pharmaceutical Development Information	No required	Required
DS Characterization	Some data in early IND	Full characterization
Specifications for DS and DP	Tentative acceptance criteria from a few small IND batches	Established acceptance criteria based on multiple pilot- or full-scale batched and statistical analysis
Validation of Analytical Procedures	Scientifically sound analytical procedures wo/ full validation	Full validation required
Impurities	Identification	Identification and qualification
Process Validation	No required	Can be completed after NDA approval
Stability Protocols	Detailed protocol not needed for P1	Required detailed protocol
Stability Data and Shelf Life	Data to support the duration of clinical studies during IND phase	Data to support the shelf life

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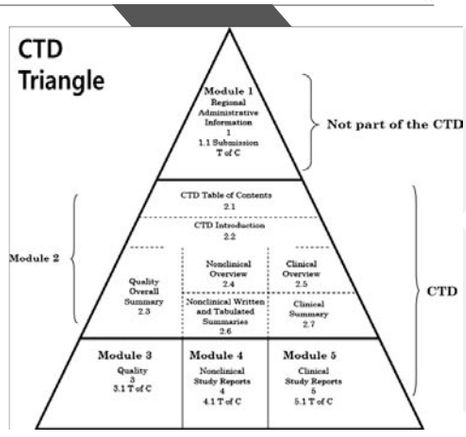
CTD Triangle and Module 3 - Quality

CTD Triangle
– ICH M4 Guidance: Organization of the Common Technical Document (CTD)
– Harmonization effort to align structure and content of NDAs – 5 Modules

Module 3 – Quality
– Diverse team of CMC experts (SMEs; Subject matter experts) – With a wide variety of expertise and experience
– Health authority meetings and minutes
– Review questions and experiences
– Inspection questions and experiences
– Prepare complex documents which meet reginal and global standards



The ultimate goal is to provide the Heath Authority with a reviewer-friendly CTD so that the focus of their review is content, not on the format

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