GMP Aspects of NCE Development for early phase INDs – CMC Perspective

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Overview

- Introduction
- GxP in Drug Development
- Regulatory Focus and Approach
- Regulatory legal framework & Global practices
- Early phase GMP challenges
- CMC Development & Concerns
- Conclusion
Introduction

R&D time and Drug Attrition rates in India

<table>
<thead>
<tr>
<th>Phase</th>
<th>Compounds</th>
<th>Success rate</th>
<th>Timelines</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preclinical</td>
<td>214</td>
<td>82</td>
<td>1.9</td>
</tr>
<tr>
<td>Phase-I</td>
<td>63</td>
<td>34</td>
<td>2.5</td>
</tr>
<tr>
<td>Phase-II</td>
<td>23</td>
<td>4</td>
<td>3.4</td>
</tr>
<tr>
<td>Phase-III</td>
<td>3</td>
<td>1</td>
<td>3</td>
</tr>
</tbody>
</table>

Edmond Differding, ChemMedChem 2017
Drug Development: Risk based Approach

- Pre-GMP
- Increasing CGMP Expectations

- R&D
- Pre-clinical (Tox)
- Phase 1
- Phase 2a
- Phase 2b
- Phase 3
- Commercial

- Apply GDPs
- Apply GLPs
- Apply Basic GMPs
- Apply Full GMPs

- Increasing Process/Product/CMC Knowledge and Understanding

- Process Validation
- Bioburden and Endotoxin Controls
- Qualified Analytical Methods
- Validated
- Calibrated Equipment
- Calibrated and Qualified Equipment
Drug Development Pathway

Drug Discovery Research
- Synthesis for drug discovery
- Lead compound optimization
- Biological evaluation
  - in vitro / in vivo
- Pharmacokinetics/Pharmacodynamics
- Physical properties
- General pharmacology
- Safety
- Biomarker research

New drug candidates

Screening

Research and Development
- API supply / Investigational drug manufacturing
- Process chemistry research
  - Formulation research
  - Physical properties analysis and research
- Safety research
  - Pharmacokinetics/Pharmacodynamics
  - Drug development research for efficacy
- General pharmacology
- Biomarker research

Clinical research
- Phase I studies
- Phase II studies
- Phase III studies

Non-clinical research

Submission

Review

Approval
- Drug use results survey
- Clinical studies after approval
- Drug-drug interaction studies
- Compatibility testing
- Build Safety Database

Drug fostering and evolution (After launch)*

Discovery research to approval

Indication expansion and new formulation development research
GxP in Drug Development Process

1. Non-clinical
   - GLP
     - Study based
     - Certified/claimed animal study ethics committee approval (Each Study)

2. Material for clinical trial DS/DP
   - GMP
     - Process based
     - Permission/license for production each product/not each batch
     - Material quality
     - Safety first
     - Efficacy next
     - CMC increasing control

3. Clinical trials phase I to III
   - GCP
     - Study based
     - Facility approval ethics committee approval (Each Study)

4. Commercial DS/DP
   - GMP
     - Process based
     - Permission/license for production each product/not each batch
     - Material quality
The early phase development and manufacturing is a balance between risk acceptance and risk mitigation.

But of what risk are we speaking?
- To the patient?
- To the manufacturing process?
- To further product development / commercialization?
- To the study reliability?

What do we want:
- Safe product
- Meaningful results
- Further development is built on data driven knowledge

The objectives of trials should guide the objectives in manufacturing and development.
R&D / Phase I / Phase II / Phase III / Pre - Commercialization
Quality / GMP expectations for Drug Substance applied by Phase of development
Good Research and Documentation Practices
GLPs Pre-Clinical (Tox assessment)
Early Phase cGMP expectations
Calibrated equipment / Qualified equipment
Qualified Methods / Validated Methods
Process validation
Pre-Commercialization cGMP expectations
Process Understanding - QbD
Risk-Based/Science-Based Approach to compliance decisions ICH Q8/Q9/Q10

Quality and Compliance expectations increase along with Drug Development timeline
Quality systems are similar but not the same
- Key stakeholder differ in their roles and responsibilities
- Outputs are not similar- report versus material
- Compliance, data integrity and quality of work are common
Regulatory Approach

- Drugs including investigational new drugs are required to be manufactured in accordance with CGMPs
  - If not, considered adulterated [501(a)(2)(B) Food, Drug and Cosmetic Act]


- Specific regulations for GMP production
  - Q7A GMP Guidance for Active Pharmaceutical Ingredients
Regulatory Legal Framework

FDA Guidance for Phase 1 INDs:
Recognizes some controls and the extent of controls differ between investigational and commercial manufacturing, as well as phases of clinical studies

• Phase I Guidelines – 1991 : Doesn’t not cover all manufacturing situations of IMP adequately

CGMPs for Phase-I (2008)
• Recommendations that provide flexibility to the manufacturers in implementing CGMP controls appropriate to their specific situation and application.
  • Exempt from compliance
  • Exempt from process validation

CGMPs for Phase-II/III
• Applicability of 21 CFR part 210 & 211
• Process controls
# Global Regulatory Practices

<table>
<thead>
<tr>
<th>ICH</th>
<th>EU</th>
<th>DCGI</th>
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</table>
| [501(a)(2)(B) Food, Drug and Cosmetic Act]  
- CGMP for phase I investigational drugs  
- INDs for Phase 2 and Phase 3 studies: Chemistry, manufacturing and controls  
- ICHQ7 for good manufacturing practices  
  - Section 19  
- Other Q & S series and M7 | Directive 2003/94/EC (for medicinal products and IMP for human Use)  
- EC GMP-Guide (detailed guidance)  
  - Part I (Finished products) + Annex 13 (IMPs)  
  - Part II section 19 (APIs for use in clinical trials)  
- EC : EudraLex-Volume 4 (GMP) and Volume 10 (CT material) | Drugs and cosmetic act 1940 from CDSCO  
- Schedule-M  
  - Emphasis mainly on commercial manufacturing  
- New Drugs and Clinical Trials Rules 2019 G.S.R. 227(E) |
# Early Phase GMP Challenges

<table>
<thead>
<tr>
<th>Aspect</th>
<th>IND</th>
<th>Commercial</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>GMP requirements</strong></td>
<td>Scope and extent may vary, no uniform common regulations, change agency wise, clear guidelines missing in certain areas, applied at appropriate stages</td>
<td>Applicable – scope and extent detailed, uniform common requirements principally, each agency advocates common minimum requirements and applied at all the stages</td>
</tr>
<tr>
<td><strong>Information</strong></td>
<td>Limited, as the stage and state are exploratory.</td>
<td>Adequate, detailed as stage and state is established.</td>
</tr>
<tr>
<td><strong>Scale of manufacturing</strong></td>
<td>Small scale</td>
<td>Full scale</td>
</tr>
<tr>
<td><strong>Toxicity</strong></td>
<td>Limited data</td>
<td>Toxicity qualified</td>
</tr>
<tr>
<td><strong>Process</strong></td>
<td>Non-repetitive, critical parameters not fully known</td>
<td>Proven acceptable ranges and critical parameters established, consistent</td>
</tr>
<tr>
<td><strong>Production</strong></td>
<td>Lack of fixed routines, package designs</td>
<td>Planned routine production, fixed packages and designs</td>
</tr>
<tr>
<td><strong>Labelling</strong></td>
<td>Blinding is a necessary aspect</td>
<td>Always open</td>
</tr>
<tr>
<td><strong>Validation (Analytical &amp; Process)</strong></td>
<td>More emphasis on verification</td>
<td>All aspects of validation covered</td>
</tr>
<tr>
<td><strong>Material Requirements and attributes</strong></td>
<td>Limited data and knowledge in terms of API as single batch may be used</td>
<td>Better data base as multiple API batches are used.</td>
</tr>
</tbody>
</table>
## GMP and Quality at Development stages

<table>
<thead>
<tr>
<th>System</th>
<th>R &amp; D</th>
<th>Toxicology</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
</tr>
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<tbody>
<tr>
<td>QUALITY:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>• Quality management systems</td>
<td>• Notebook records are kept of production and testing activities</td>
<td>• GLP practices are implemented as per regulation in specific global regions.</td>
<td>• CGMP (e.g. ICH Q7 and Annex13).</td>
<td>• QA involvement by phase of development</td>
<td>• Quality standards</td>
</tr>
<tr>
<td>• Personal Training</td>
<td>• Quality by Design Principles should be applied to the selection, development and qualification</td>
<td>EU and FDA GLP requirements cover the area of</td>
<td>• Summary development reports.</td>
<td>• The bulk Drug Substance is released by QA</td>
<td></td>
</tr>
<tr>
<td>• Documentation and records</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Change management</td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>• Deviations/Investigations</td>
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<td></td>
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<tr>
<td>• CAPA</td>
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<td></td>
<td></td>
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<tr>
<td>• Auditing</td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>• Quality Agreements</td>
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</table>

- Change management
- Specifications
CMC Regulatory requirements at IND stages

Regulations emphasize the graded nature of CMC information needed as drug development progresses under an IND

- The amount of information needed depends on Phase of investigation
- Dosage form
- Duration of study

FDA recognizes that CMC development parallels clinical investigations

- Primary objective is to assure the safety of patients, during all phases of the IND
- Phase 1 CMC evaluated mainly from the point of risk to patient.
- Phase 2 and 3 CMC evaluates safety, and additionally the linkage of the clinical test product to the to-be-marketed product
## CMC Regulatory requirements at IND stages

<table>
<thead>
<tr>
<th>Phase - 1</th>
<th>Phase - 2 &amp; 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Safety is the main concern which is addressed with pharm/tox data</td>
<td>Safety updates on the information provided for phase 1</td>
</tr>
<tr>
<td>Drug substance has been tested, thus impurity profile and potency are known in animals</td>
<td>Impurities should be identified, qualified and quantified</td>
</tr>
<tr>
<td>Sufficient evidence to support chemical structure</td>
<td>More detailed description of the configuration and chemical structure for complex organic compounds</td>
</tr>
<tr>
<td>Brief description including physical, chemical and biological properties</td>
<td>Complete description of the physical, chemical and biological characteristics</td>
</tr>
<tr>
<td>Reference standard establishment</td>
<td>Reference standard qualification</td>
</tr>
<tr>
<td>Established specification based on tox and assurance batches.</td>
<td>Suitable limits based on manufacturing experience should be established</td>
</tr>
<tr>
<td>Drug substances and products are manufactured according to CGMP for Phase 1 IND</td>
<td>Drug substances and products are manufactured according to CGMP for Phase 2&amp;3</td>
</tr>
<tr>
<td>Brief description of stability study and analytical procedure used</td>
<td>Detailed stability study and stability indicating analytical methods to be used</td>
</tr>
</tbody>
</table>
Relationship between GMPs and CMC Requirements

- The regulatory strategy used to ensure pharmaceutical product quality involves both CMC and GMP oversight.
- CMC requirements set the criteria and controls for manufacturing and testing, as described in the submission or dossier.
- GMP requirements are derived from the regulations and guidelines pertaining to the implementation of practices and standards in a manufacturing facility that allows for the consistent production of a quality product with the intended purity, safety and potency characteristics.
Synergy of GMP and CMC

**Focus:**

**Industry Role:** Setting manufacturing quality criteria and controls

**Guidance:** ICH Q1-6, M4

**Agency Role:** Assessment and Approval of manufacturing and Quality standards and controls

**Submission/Dossier**

Implementing manufacturing and testing practices designed to meet manufacturing and Quality Standards

**Facility/Manufacturing/Testing**

ICH Q7

Verification of conformance to CGMP and to regulatory submission/dossier standards through facility Inspections; Evaluation of Quality system

**ICH Q8-10**
Because they are both critical pillars of product quality, there are often areas of overlap between CMC considerations and GMPs.

Examples of areas of overlap include:
- Process development
- Validation
- Continuous process improvement.

Resolution of the overlap can be achieved by viewing CMC development as a “process, criteria and controls setting activity” and GMPs as an “implementation activity”
CMC Concerns

- Reasons for selection, stability, physicochemical properties of various forms

Polymorphs

- No agreement on starting material
- Lack of information on key starting materials

Key starting materials

- Insufficient stability data
- Unstable Molecule
- No Stability indicating method

Stability

- In-process controls
- Reproducibility issue
- Inconsistent data between lot to lot
- Manufacturing variability

Safety

- Inadequate control of impurities from KSMs
- Impurities not covered in tox
- Mutagenic impurities at higher levels
- Lack of control strategy to limit impurities

Impurities

- Manufacturing variability
Clinical Hold

- Unknown or Impure component's
- Chemical structure of known or highly likely toxicity
- Product that can't remain chemically stable for throughout the testing program proposed
- Product with an impurity profile indicative of a potential health hazard or impurity profile insufficient defined to assess potential health hazard
- Poorly characterized reference standard
- Process control strategy for process degradants
How to overcome Failures

Drug Failures related to clinical safety, quality, efficacy, safety issues w.r.t. API and Drug product can be overcome by establishing control strategy of the Drug from starting to ending
# CMC Development Elements

## Deliverables

<table>
<thead>
<tr>
<th>Product Understanding</th>
<th>Process Understanding</th>
<th>Control Strategy</th>
<th>Control Strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quality Target Product Profile</td>
<td>Critical Quality Attribute Assessment</td>
<td>Process Performance Indicators</td>
<td>Process Controls Control of DS &amp; DP In process testing Container systems</td>
</tr>
<tr>
<td>Intended use Route Dosage</td>
<td>Impurities Particle size stability</td>
<td>PPIs and Ranges</td>
<td>Process controls Control of DS &amp; DP In process testing Container systems</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Characterization Plan</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Characterization Data</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>CPPs / CRMs/ CMAs and Ranges</td>
<td></td>
</tr>
</tbody>
</table>

- **Product Understanding**:
  - Define desired quality characteristics of the product
  - Perform risk assessment to link quality attributes to Clinical Safety and Efficacy
  - Study the impact of deliberate variation in process parameters and raw materials (inputs) on proposed CQAs and determine process parameter and raw material criticality
  - Derived based on understanding and control of sources of variability to ensure product Quality and Consistency
Conclusion

- Graded nature of CMC information from Phase 1 to Phase 3 studies.
- CGMP should be applied for Phase 1 drugs do not need full CGMP but do need good manufacturing controls.
- IND regulatory oversight focused on safety as primary review objective.
- Amount of CMC information depends on the phase of IND, duration of study.
- Need for a harmonized drug regulations globally, especially the regulatory requirements for fastening the lengthy drug development for unmet medical needs.
Indian Pharmaceutical Alliance

Thank You