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Innovation, Quality and Global Reach

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

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Overview

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

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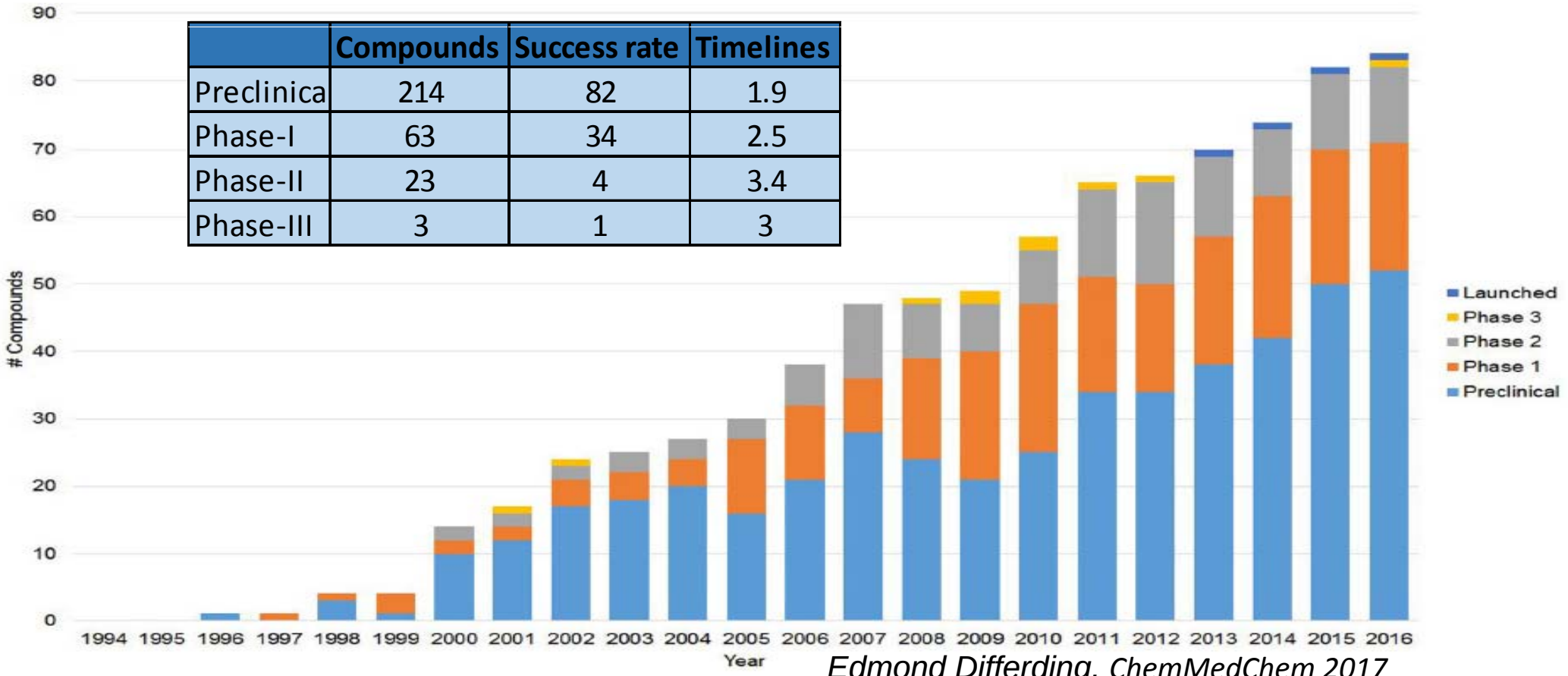
Introduction

R&D time and Drug Attrition rates in India

	Compounds	Success rate	Timelines
Preclinica	214	82	1.9
Phase-I	63	34	2.5
Phase-II	23	4	3.4
Phase-III	3	1	3



Edmond Differding, ChemMedChem 2017

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Introduction *contd...*

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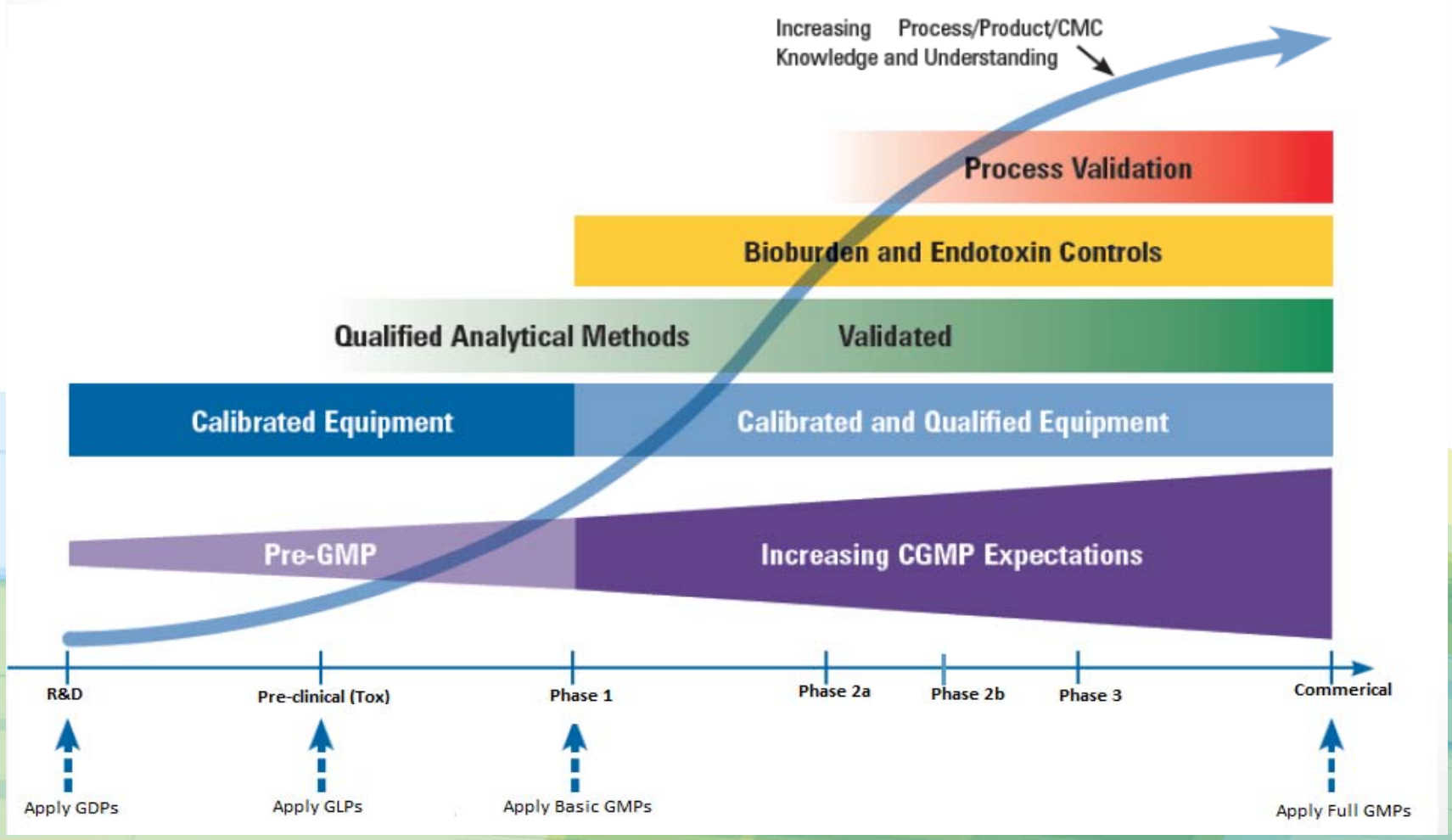
Drug Development : Risk based Approach



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Drug Development Pathway

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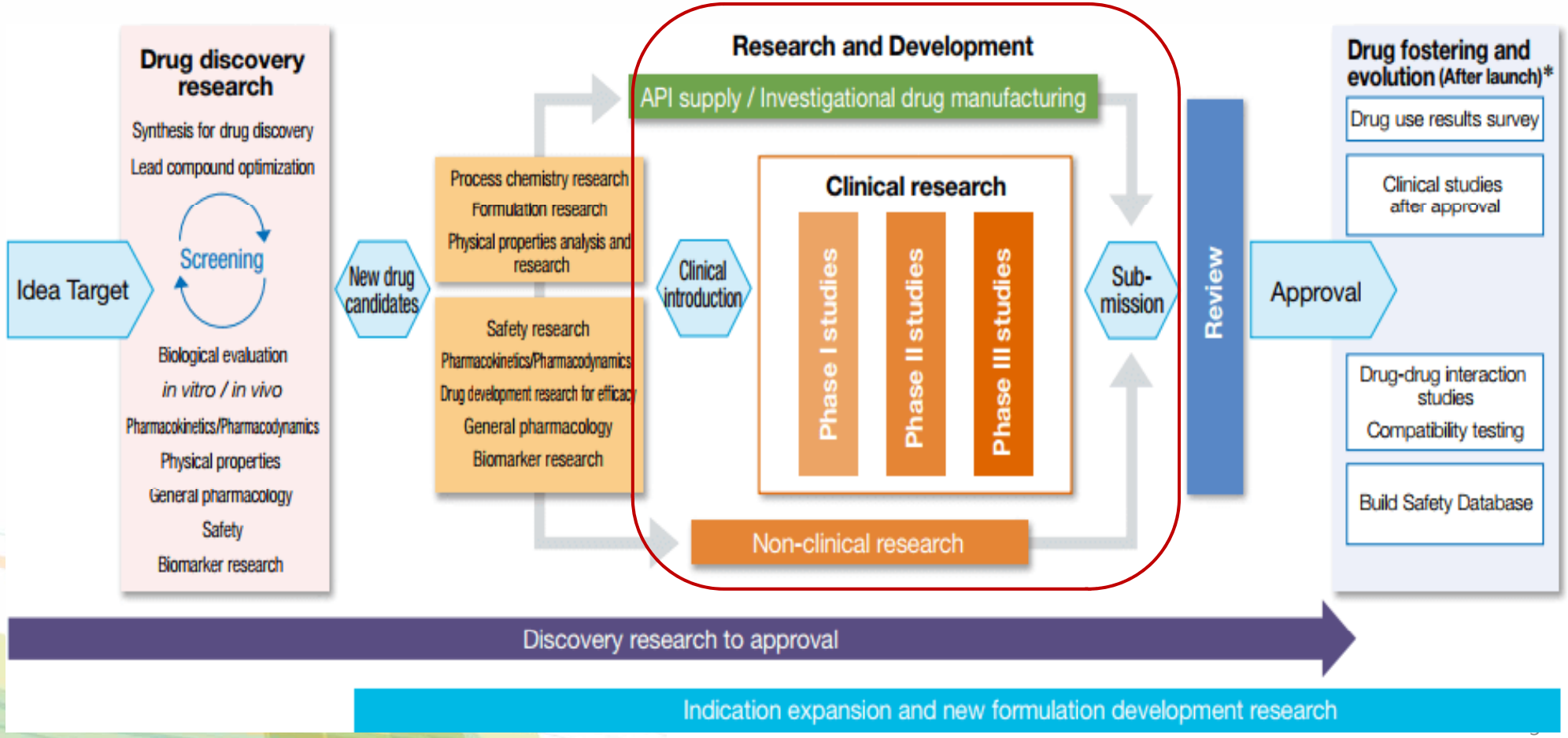

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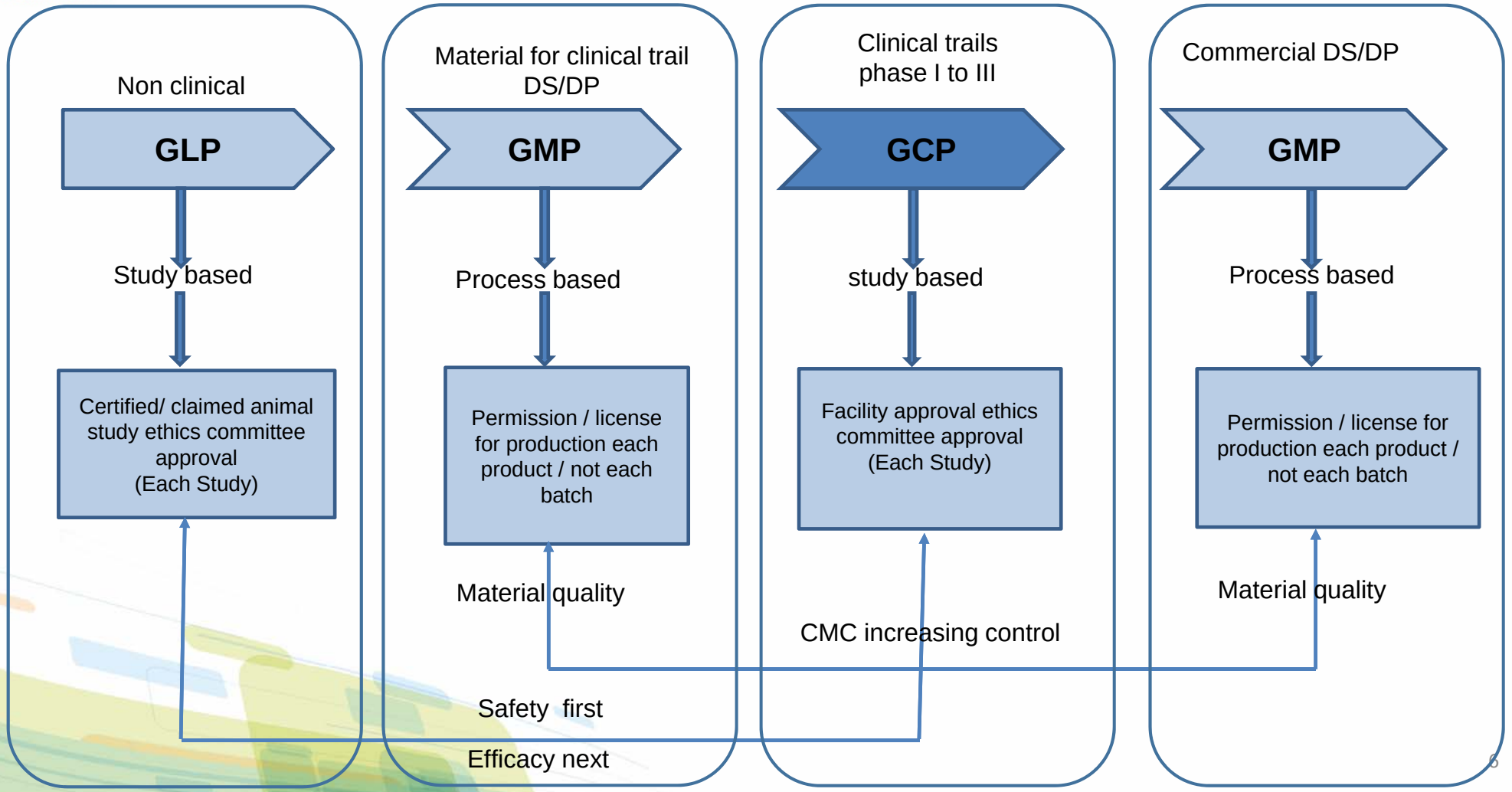
GxP in Drug Development Process



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Regulatory Focus

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- 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

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Regulatory Focus *Contd.*

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- 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

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Common Regulatory Creep

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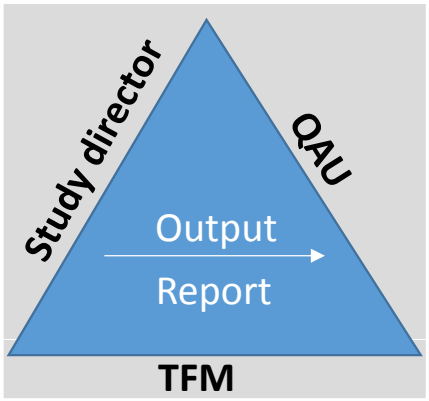
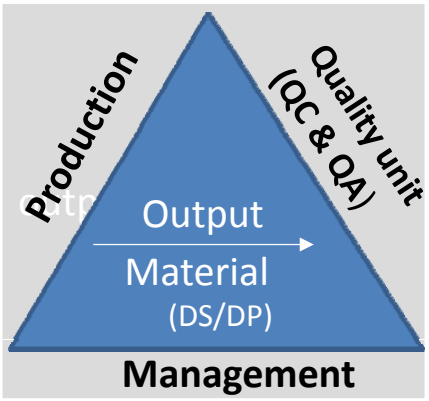
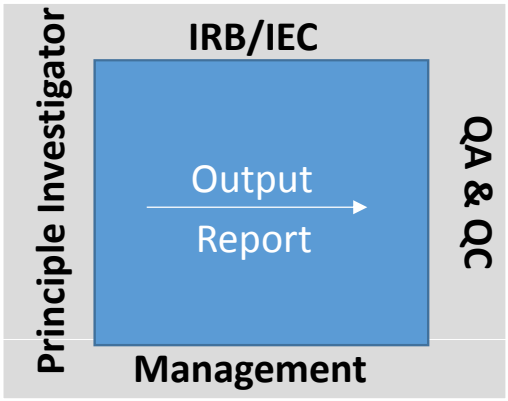
GLP



GMP



GCP



- **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**

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Regulatory Approach

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- **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]
- **21 CFR 210, 211 Current Good Manufacturing Practices for Finished Pharmaceuticals Regulations [1978]**
- **Specific regulations for GMP production**
  - Q7A GMP Guidance for Active Pharmaceutical Ingredients

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Regulatory Legal Framework

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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

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Global Regulatory Practices

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ICH	EU	DCGI
[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)

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Early Phase GMP Challenges

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

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GMP and Quality at Development stages

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System	R & D	Toxicology	Phase 1	Phase 2	Phase 3
QUALITY: • Quality management systems • Personal Training • Documentation and records • Change management • Deviations /Investigations • CAPA • Auditing • Quality Agreements	• Notebook records are kept of production and testing activities • Quality by Design Principles should be applied to the selection, development and qualification	• GLP practices are implemented as per regulation in specific global regions. **EU and FDA GLP requirements cover the area of** ✓ Organization & personnel ✓ Facilities ✓ Equipment ✓ Facility operation ✓ Articles ✓ Protocol and conduct ✓ Records and reports ✓ Disqualifications • Laboratory director	• CGMP (e.g. ICH Q7 and Annex13). • QA involvement by phase of development • Quality standards • Summary development reports. • The bulk Drug Substance is released by QA • Change management • Specifications		

CMC Regulatory requirements at IND stages

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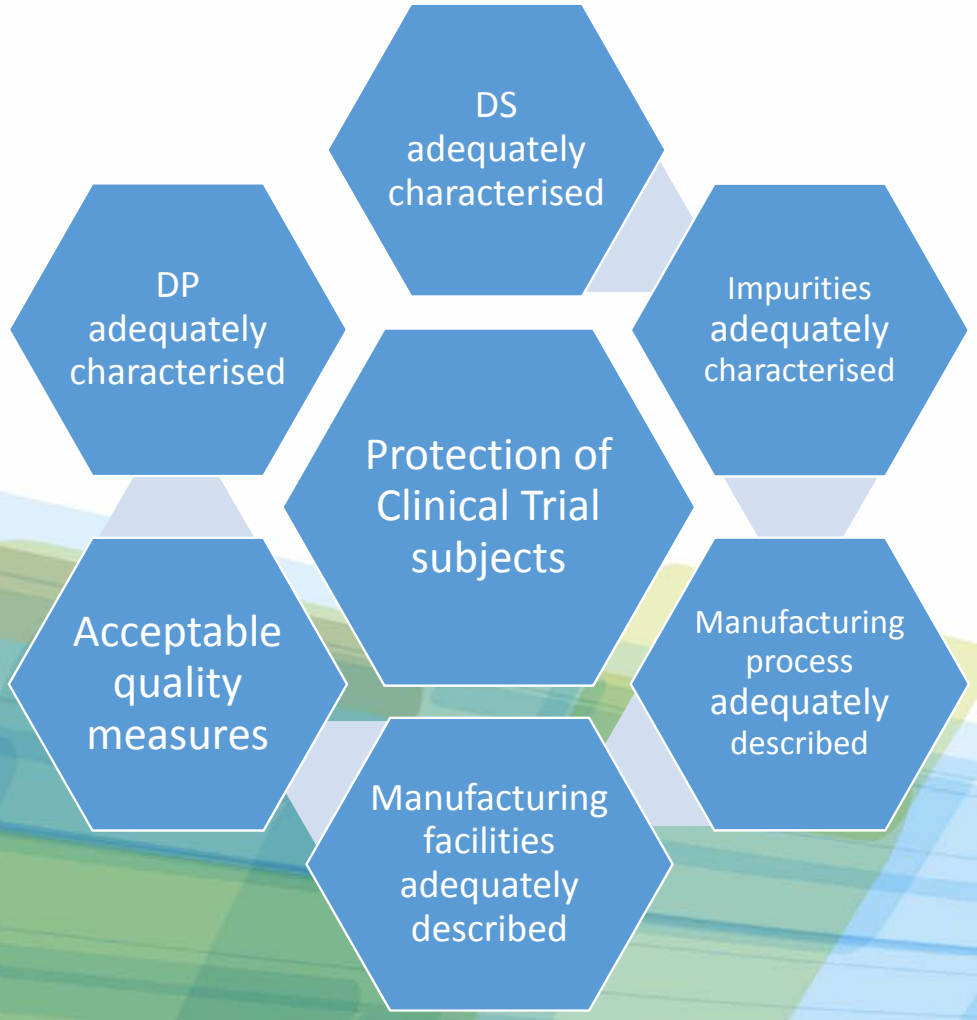
Regulations emphasize the graded nature of CMC information needed as drug development progresses under an IND

- 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



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CMC Regulatory requirements at IND stages *Contd.*

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

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Relationship between GMPs and CMC Requirements

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- 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

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Synergy of GMP and CMC

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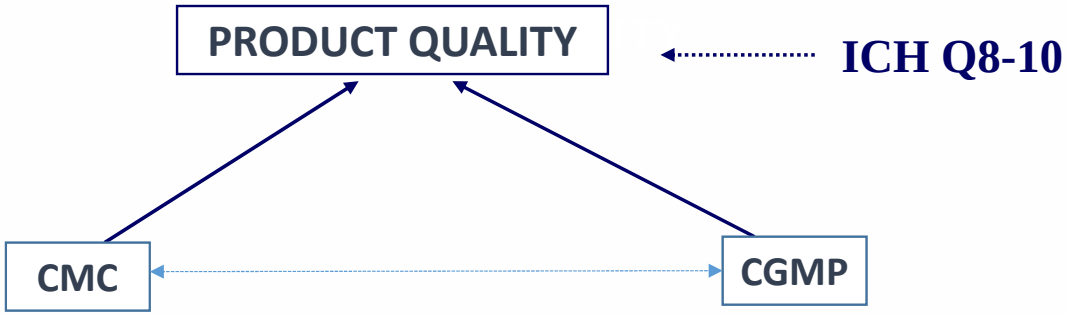

Focus:	Submission/Dossier	Facility/Manufacturing/Testing
Industry Role:	Setting manufacturing quality criteria and controls	Implementing manufacturing and testing practices designed to meet manufacturing and Quality Standards
Guidance :	ICH Q1-6, M4	ICH Q7
Agency Role :	Assessment and Approval of manufacturing and Quality standards and controls	Verification of conformance to CGMP and to regulatory submission/dossier standards through facility Inspections; Evaluation of Quality system

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GMP Creep into CMC

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- 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”

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CMC Concerns

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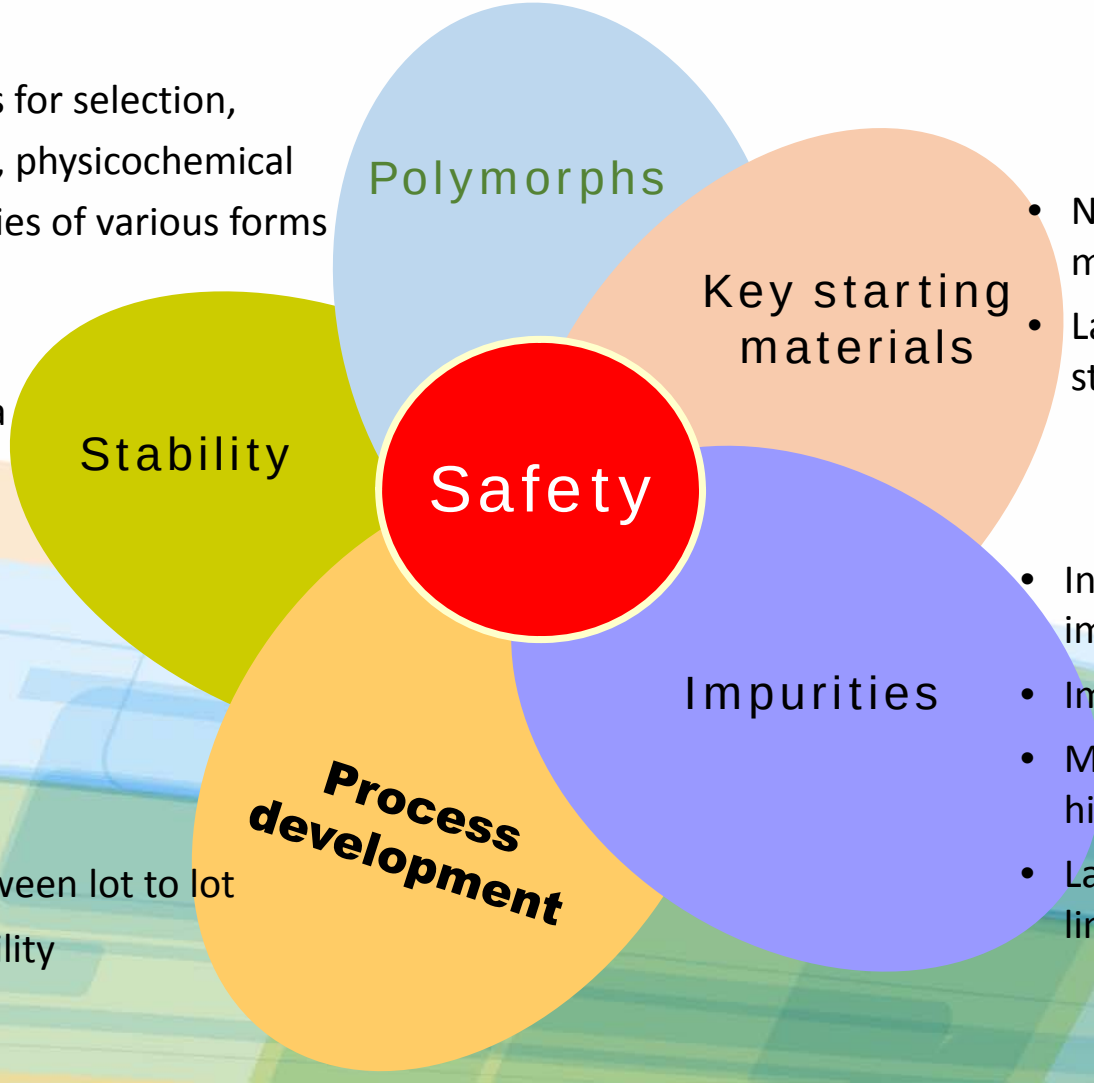

- Reasons for selection, stability, physicochemical properties of various forms

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

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

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

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

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Clinical Hold

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- Unknown or Impure component's
- Chemical structure of known or highly likely toxicity
- Product that cant remain chemically stable for through out 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

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How to overcome Failures

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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

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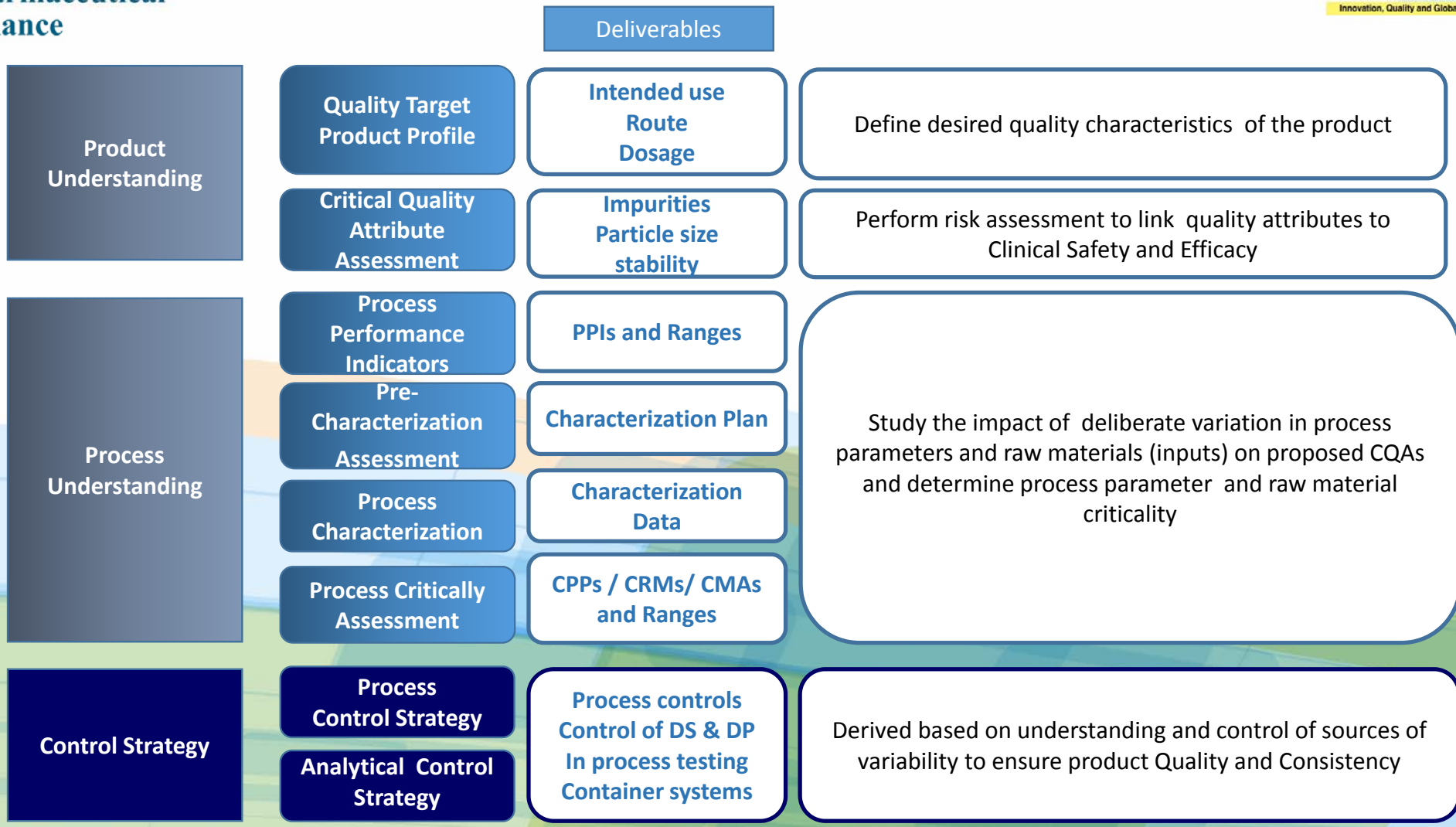

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Conclusion

- 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

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Thank You