The landscape of CTD submission package from RD stage to commercialization: a storytelling prospective

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Disclaimer

- This presentation contains a summary of opinions and perspectives from industry representatives on the topic of “The landscape of CTD submission package from RD stage to commercialization: a storytelling prospective”
- This presentation does not necessarily represent the opinion of the presenter or its employers.
- All the material included in this presentation was obtained from publicly available sources.

Roadmap of Topic / Take Home Message

- **Highlight GSubP**
  - Recap the goal and approach with GSubP
  - Timely approval and earlier patient access
- **Best practice on Generics submission preparation**
  - QTPP
  - Essence of QbD
  - Understand your product and process
  - Establish control strategy
- **Landscape of CTD preparation**
  - Readiness to collecting source material
  - Follow QbR compilation
  - Create a draft document
  - Proof reading process

- **Project management**
  - Importance of project management skill
  - Quality management
  - Keep time schedule and responsibility
- **Deficiency Response**
  - Regulatory Strategy
  - Manage timeline
  - Careful review of document
- **Training**
  - Group team effort
  - Keep knowledge up-dated
  - Sharing and learning

Good Regulatory Practice (GRP)

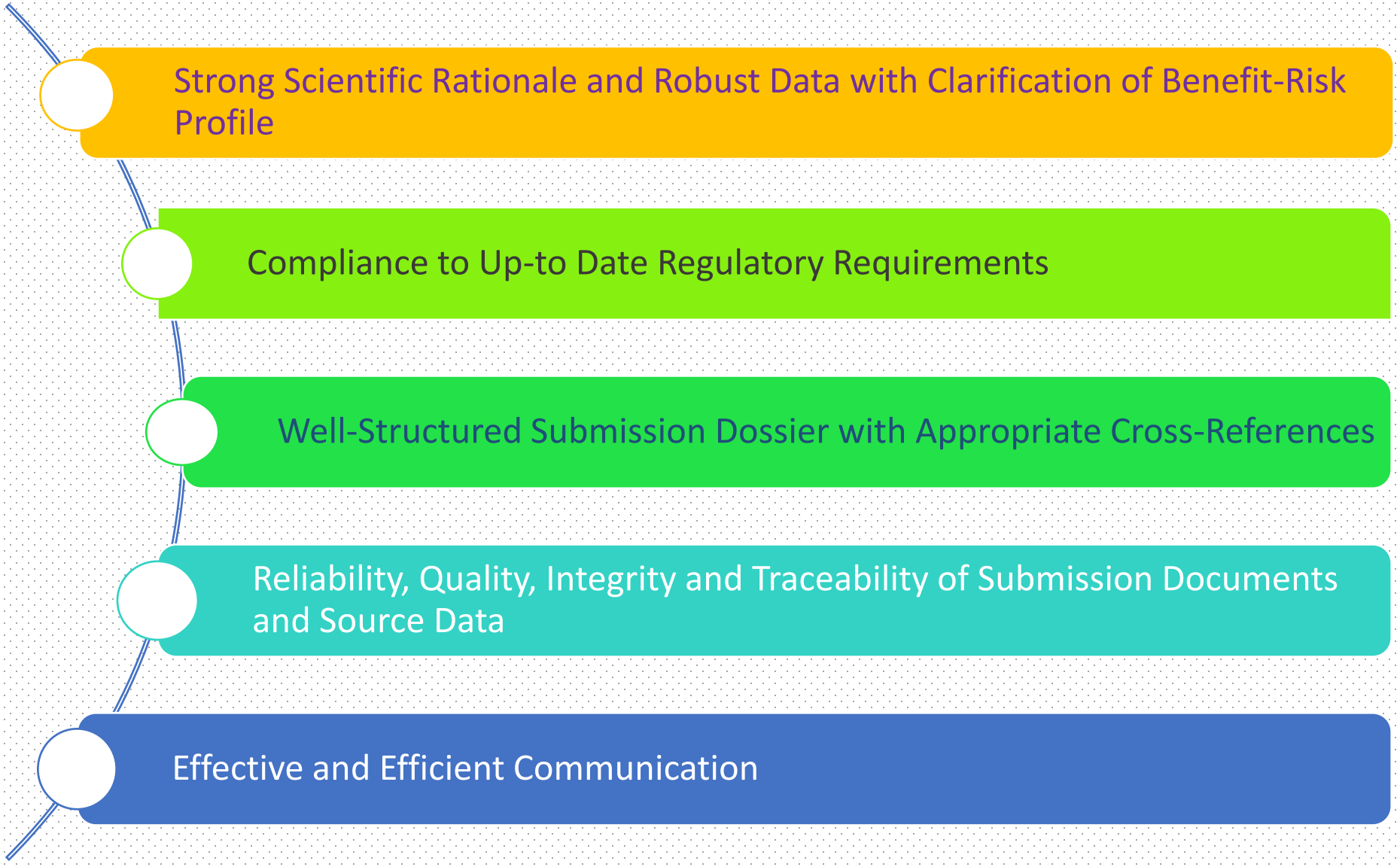
Good Review Practice (GRevP)

- Guidelines for Regulatory Authorities to improve their performance and ensure the quality of their regulatory systems
- “Documented best practices for any aspect related to the process, format, content, and management of a medicinal product review”

Good Submission Practice (GSubP)

- Guidelines for Applicant Companies to improve the quality of their submissions for registration as well as its management

Principles of Good Submission

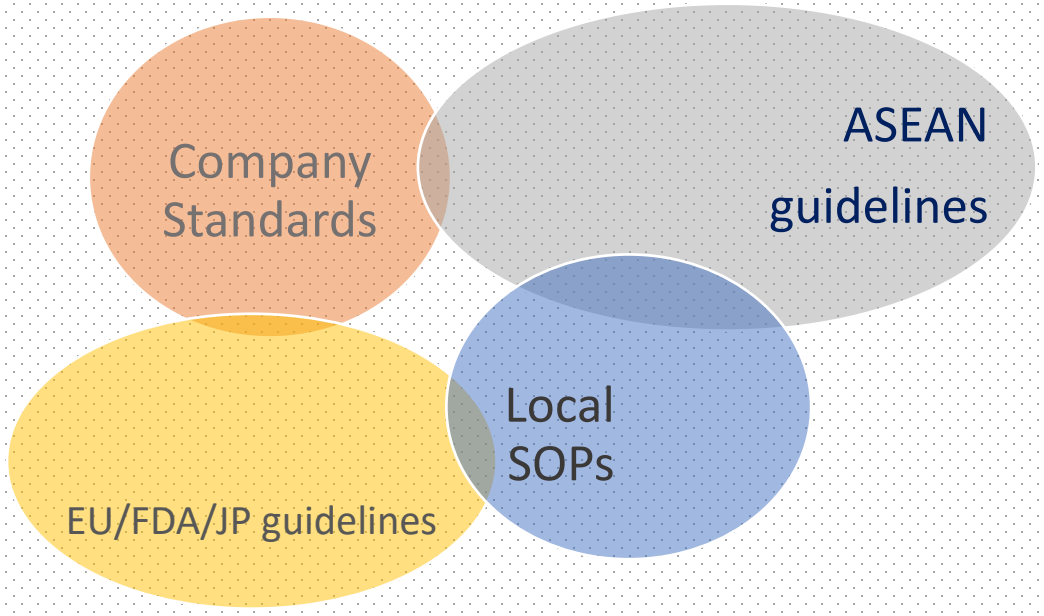


1. Strong Scientific Rationale and Robust Data with Clarification of Benefit-Risk Profile

- Rationale and data in terms of integrity, relevance and completeness
- Nature of the benefits and types of risks clarified with sound evidence

2. Compliance to Up-to-date Regulatory Requirements

- Up-to-date regulations
- Consistency with internationally harmonized regulatory standards



3. Well-Structured Submission Dossier with Appropriate Cross-references

- Well-structured dossier to comply with the acceptable format by the review authorities

ASEAN CTD

ICH CTD

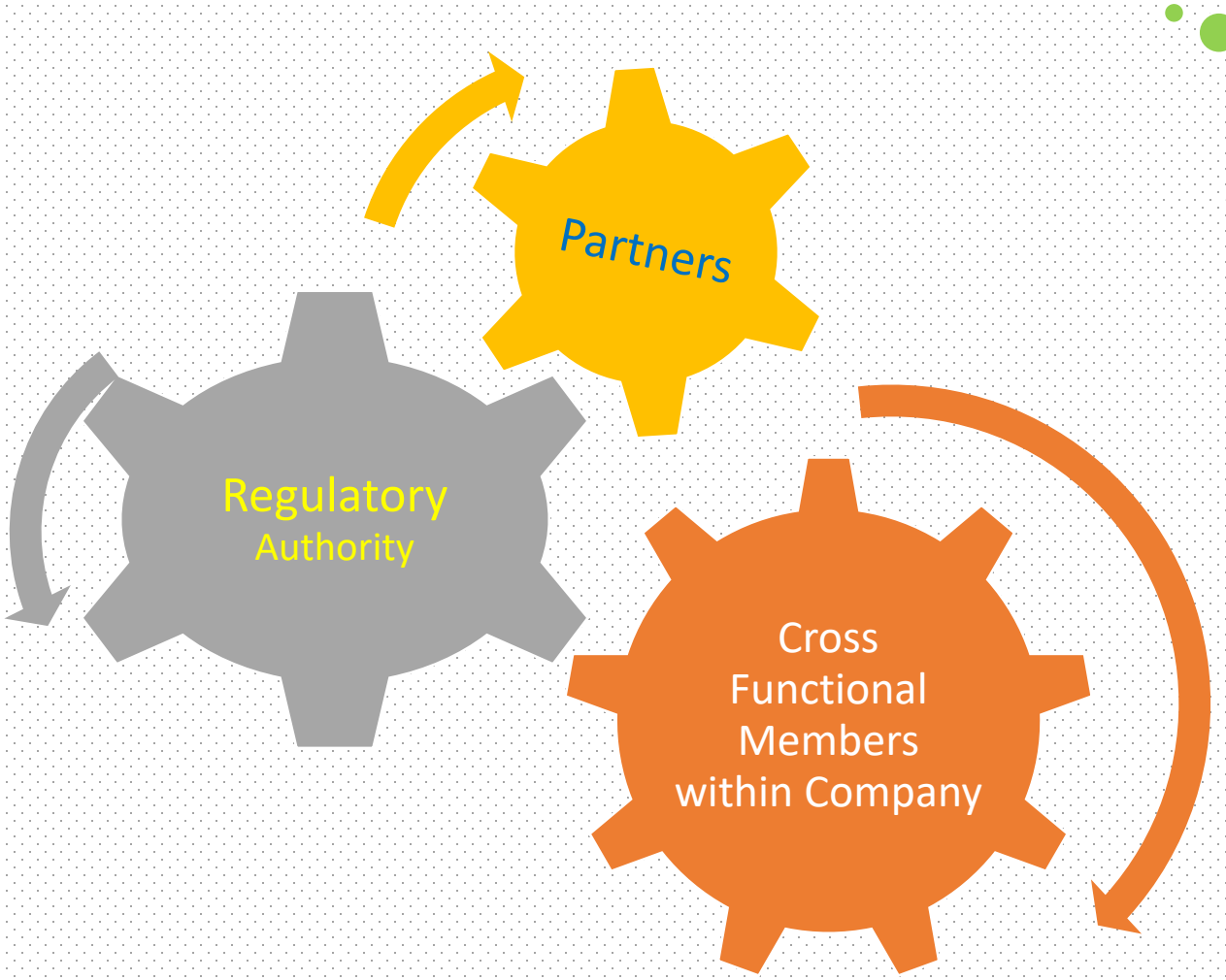
FDA Guidelines

- Applicants encouraged to use appropriate cross-references in the dossier to facilitate ease of review

4. Reliability, Quality, Integrity and Traceability of Submission Documents and Source Data

- Information and Data described in the submission documents include the reference / sources

Effective and Efficient Communication

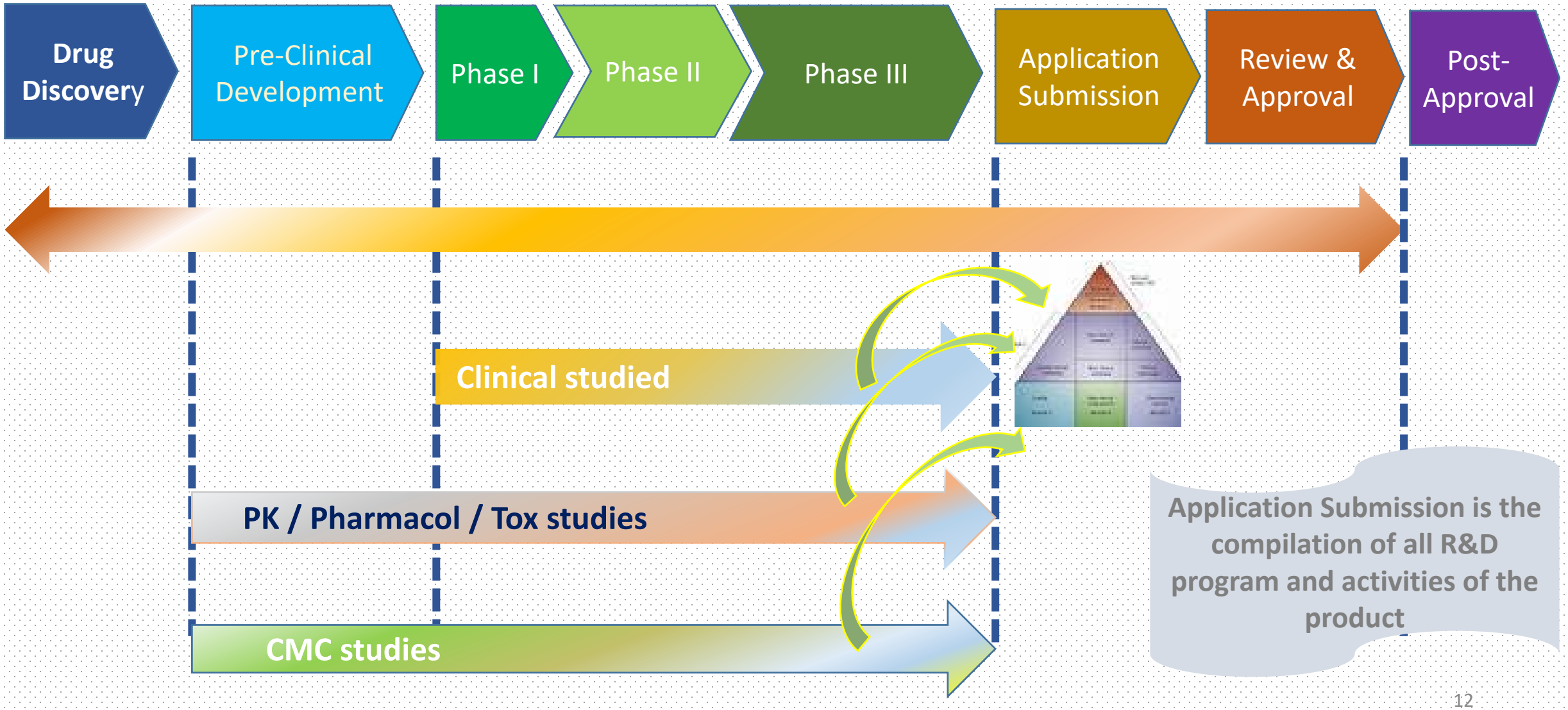


Timely approval
Earlier patient access

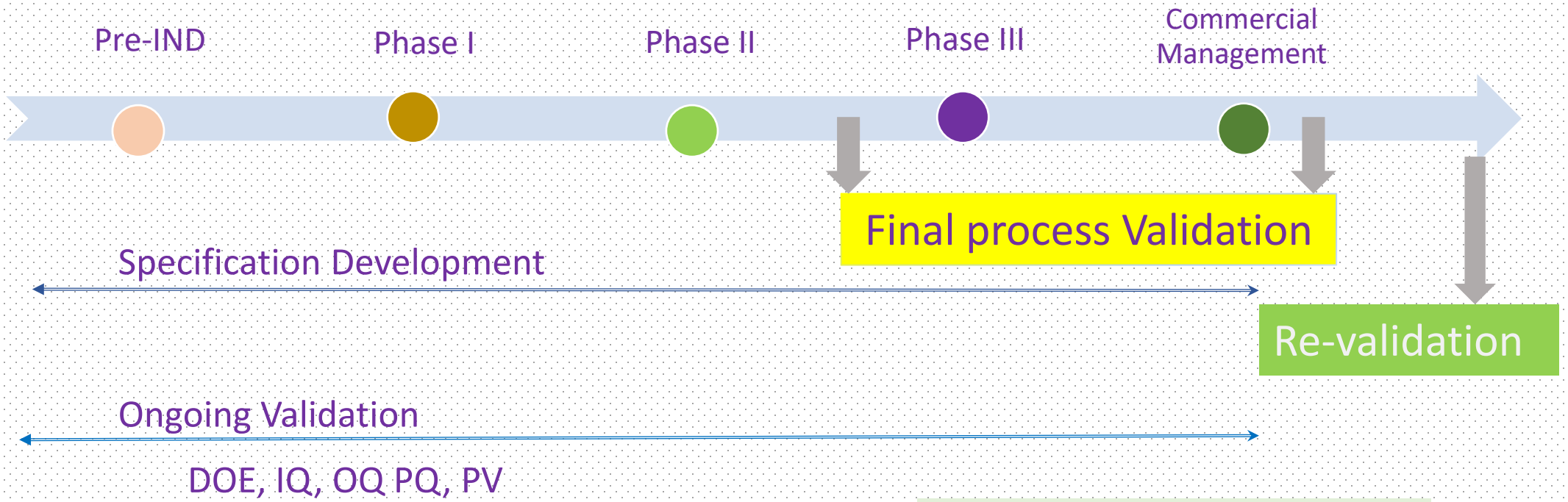
Industry Role

- **Develop methodologies to improve:**
  - Candidate selection
  - Dosage form selection and formulation design
  - Process development and optimization
  - Process control
  - Scale-up and tech transfer
  - Process validation
  - Process monitoring and continuous improvement
- **Demonstrate reduced risk to regulatory agencies**
- **Obtain regulatory relief**
- **Demonstrate value to company management**

Background of Discovery roadmap



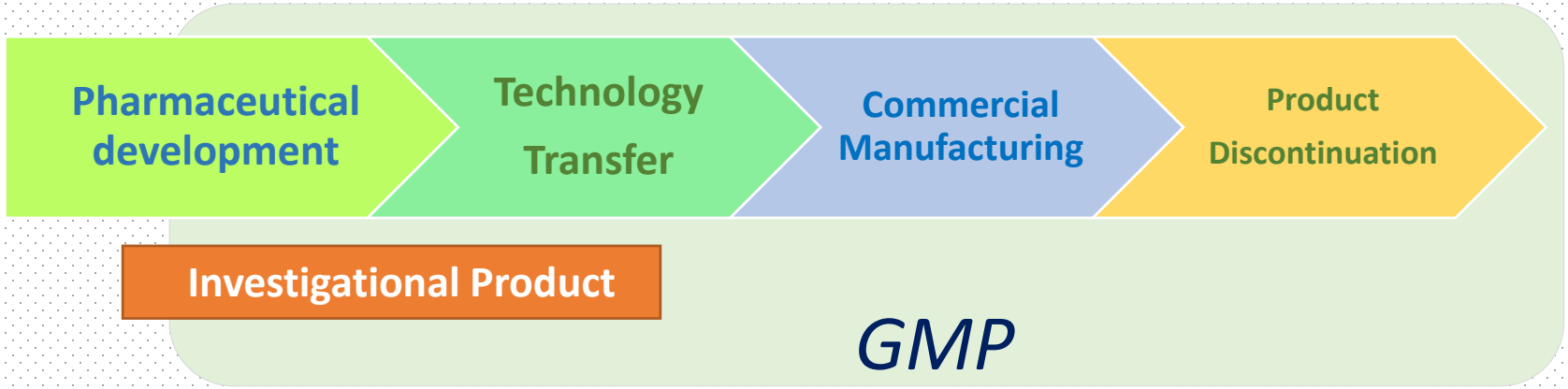
Validation is Always Part of the Picture



- The extent of IQ, OQ, PQ, validation, etc. depends on complexity of product
- 6 sigma target

DOE = Design of Experiment
IQ = Installation Qualification
OQ = Operational Qualification
PQ= Performance Qualification
PV= Process Validation

Pharmaceutical Quality System



Management Responsibility

Quality System Element

Process Performances & Product Quality Monitoring System
Corrective Action /Preventive Action (CAPA) System
Change Management System
Management Review

Element

Knowledge management

Quality Risk Management

Quality Target Product Profile (QTPP)

What is QTPP?

- A set of elements that defines the drug product
- The target or goal set in advance
- A guide to Drug Product development

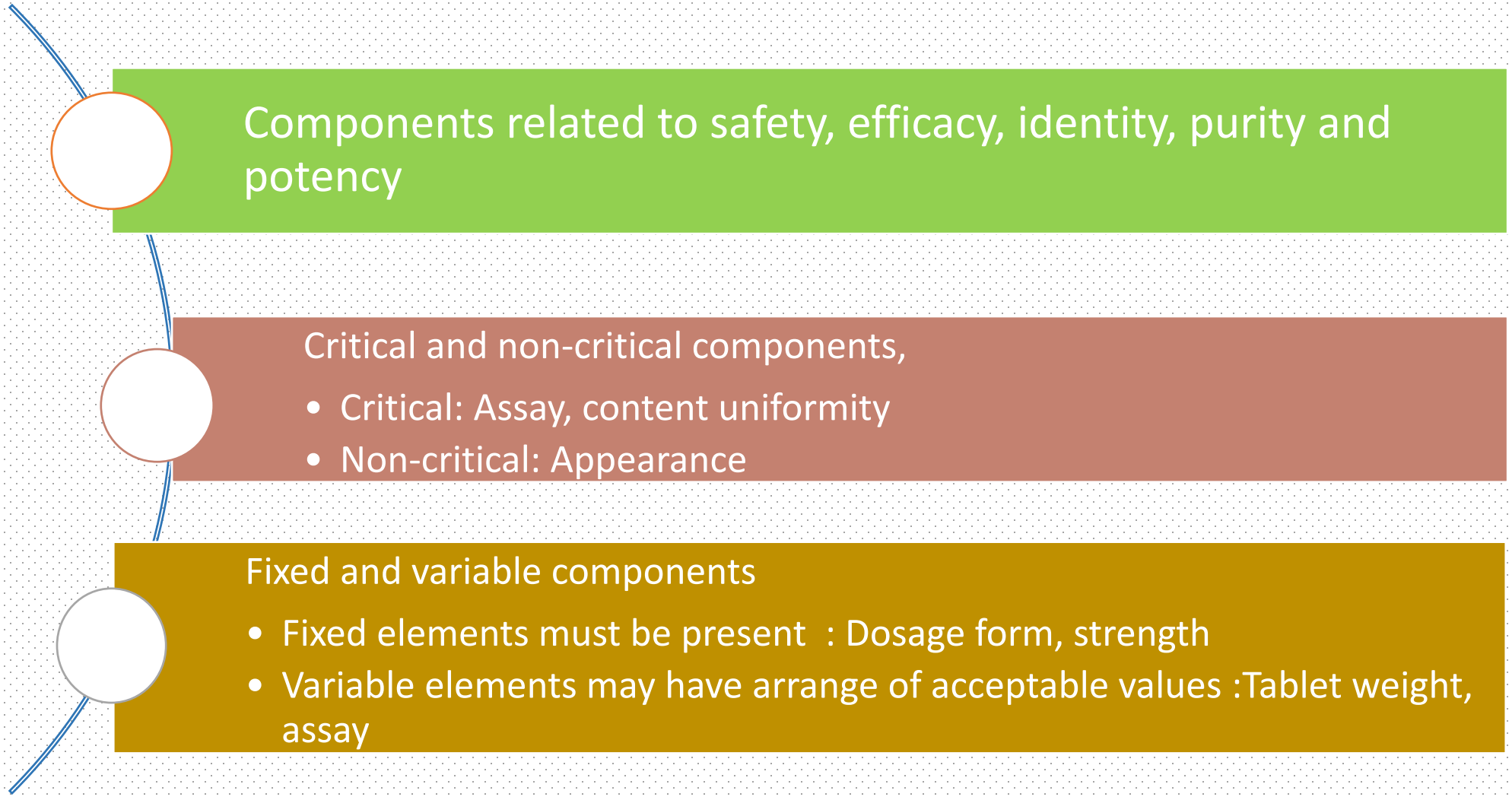
What forms the basis fro QTPP

- The RLD and its label
- Applicable regulatory guidelines

When to define QTPP

- At the start of development
- Knowledge gained in development may change some elements

Components of QTPP



QTPP components for IR Tablet (example)

QTPP IR Tablet
Dosage Form
Route of administration
Strength
Weight
Pharmacokinetics
Appearance
Identity
Assay
Impurities
Content uniformity
Friability
Dissolution
Residual solvent

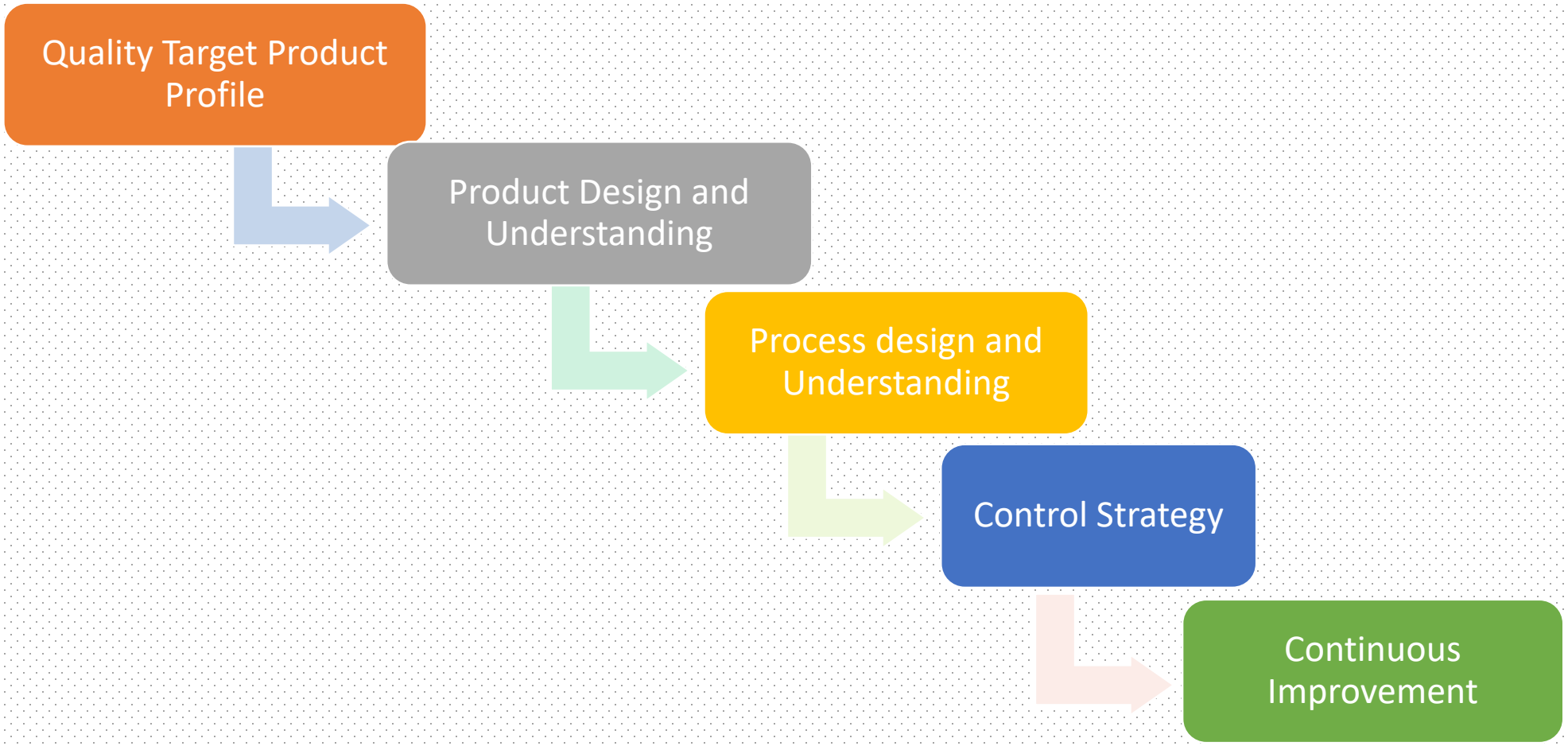
QTPP- example

Profile	Ideal	Acceptable
Target population	Both NNRTI-exposed and unexposed children less than three years old	
Dosing frequency	Once daily	Twice daily
Formulation	Water- soluble, dispersible tablet that can be used with a small amount of liquid	Sprinkles or crushable pills used in food
Pill burden	One scored pill usable across brand weight bands	If two pills, must be same tablet count (or fraction) for both
Durability	High generic barrier, long half-life	
Efficacy	Same as adults	
Safety / Tolerability	Well tolerated, and no lab monitoring needed	No lab monitoring needed
Palatability	No taste or nice taste	Palatable
Drug – drug interaction (DDI) with TB drugs	No DDI with TB drugs – particularly rifampicin/isonizide	DDIs, but overcome with simple dose adjustment
Stability	No cold chain, minimum two years self life at room temperature	
Cost	US 50 per patient year of less (consistent with adults)	To be investigated

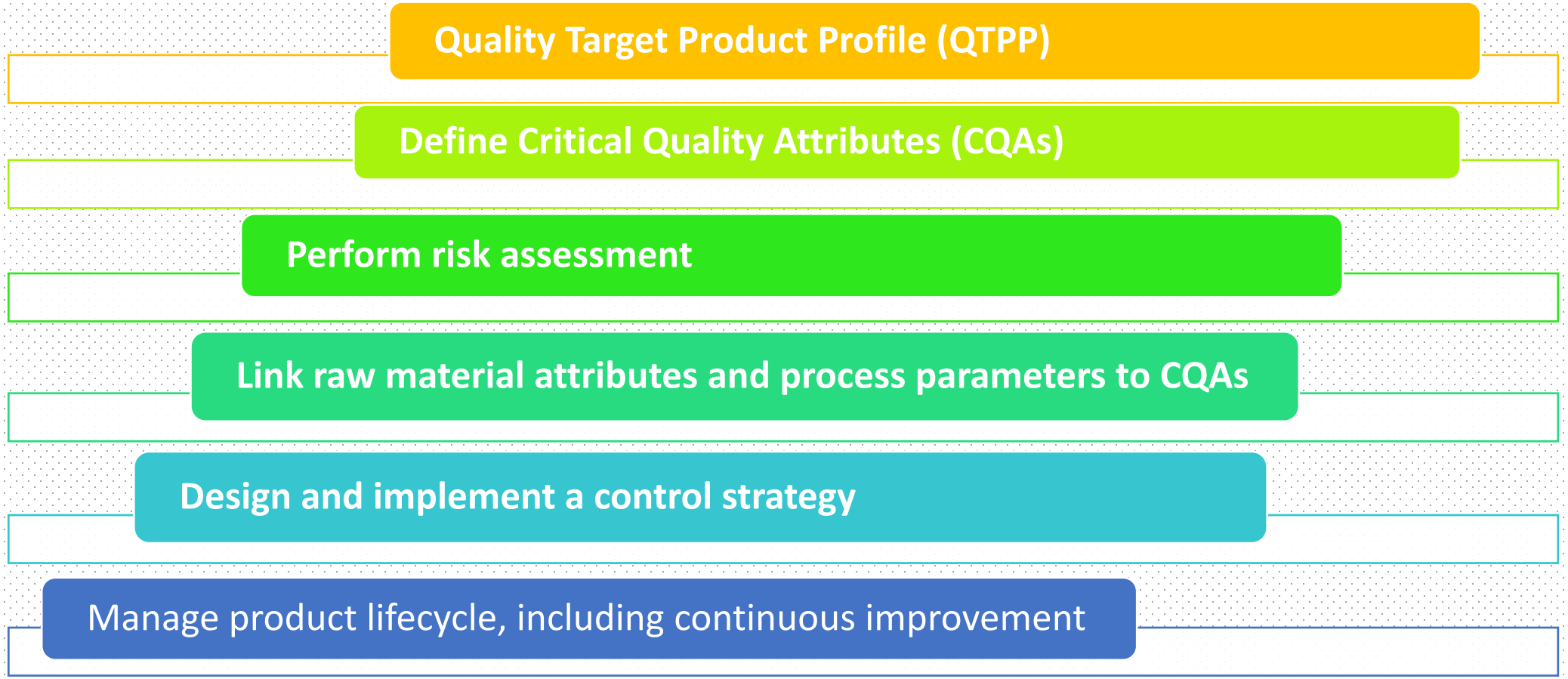
What is QbD?

ICH Q8 (R2)	Systematic, holistic and proactive approach to pharmaceutical development
	Begins with predefined objectives
	Emphasizes product and process understanding and process control
	Based on sound science and quality risk management

Overview of QbD

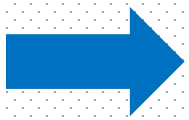


Element of QbD



QTPP and CQAs

QTPP components
Dosage Form
Route of administration
Strength
Weight
Pharmacokinetics
Appearance
Identify
Assay
Impurities
Content uniformity
Friability
Dissolution
Residual solvent



CQAs
Assay (efficacy)
Impurities (safety)
Content Uniformity (efficacy)
Dissolution (efficacy)

Risk Assessment

- Risk assessment for formulation components

Drug Product CQA	Formulation Variables				
	Drug Substance PSD	MCC/Lactose Ratio	CCS Level	Talc Level	Magnesium Stearate Level
Assay	MEDIUM	MEDIUM	LOW	LOW	LOW
Content Uniformity	HIGH	HIGH	LOW	LOW	LOW
Dissolution	HIGH	MEDIUM	HIGH	LOW	HIGH
Degradation products	LOW	LOW	LOW	LOW	MEDIUM

Risk Assessment

- Risk assessment of DP manufacturing process

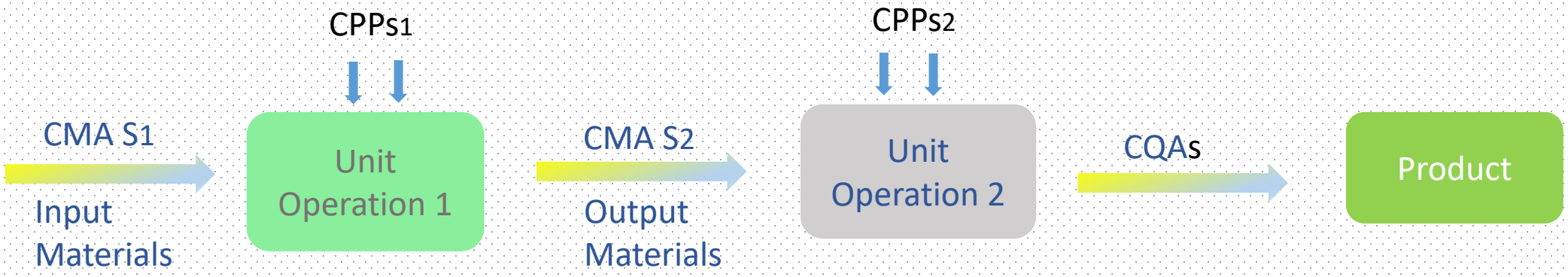
Drug Product CQAs	Process Steps				
	Pre-RC Blending and Lubrication	Roller Compaction	Milling	Final Blending and Lubrication	Compression
Assay	MEDIUM	LOW	MEDIUM	LOW	MEDIUM
Content Uniformity	HIHG	HIGH	HIGH	LOW	HIGH
Dissolution	MEDIUM	HIGH	MEDIUM	HIGH	HIGH
Degradation Products	LOW	LOW	LOW	LOW	LOW

Justification for assigned risks

Process steps	Drug Product CQAs	Assigned Risk	Justification
Pre-Roller Compaction Blending and Lubrication	Assay	MEDIUM	Suboptimal pre-roller compaction blending and lubrication may cause variable followability of the blend affecting assay
	Content Uniformity	HIGH	The PSD and cohesiveness of the drug substance adversely impact its followability. If not blended properly with excipients it may affect CU.
	Dissolution	MEDIUM	Blending process variables may impact the distribution of CCS in the blend which could impact disintegration of the granules and intimately, dissolution.
	Degradation Products	LOW	Blending process variable are unrelated to the degrading products of Generic XXX Tablets, 20mg.

CMAs, CPPs and CQAs

- What factors affect drug product CQA?
- Properties of Input Materials – Identity Critical Material Attributes (CMAs)
- Properties of in-process materials – CQAs of one step become CMAs for a downstream unit operation
- Manufacturing process parameters – Identify Critical Process Parameters (CPPs)



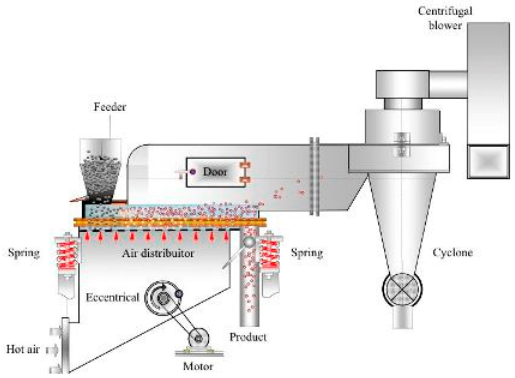
Control Strategy

- **"A planned set of controls, derived from current product and process understanding that ensures process performance and product quality… ICH Q8 (R2) & Q10**
- **Control Strategy includes following elements (but not limited to):**

Control Strategy	Input material attributes (DS, excipients, container closure)
	Equipment operating conditions (process parameters)
	In-process controls
	Finished product specifications
	Controls for each unit operations
	Methods and frequency of monitoring and control

Control Strategy

- Developing Control Strategy



Likelihood \ Impact	Very Low	Low	Medium	High	Very High
Very High					
High					
Medium					
Low					
Very Low					

CQA
CPP
CMA

Acceptance Ranges (CMA & CPP) Limits for CQA

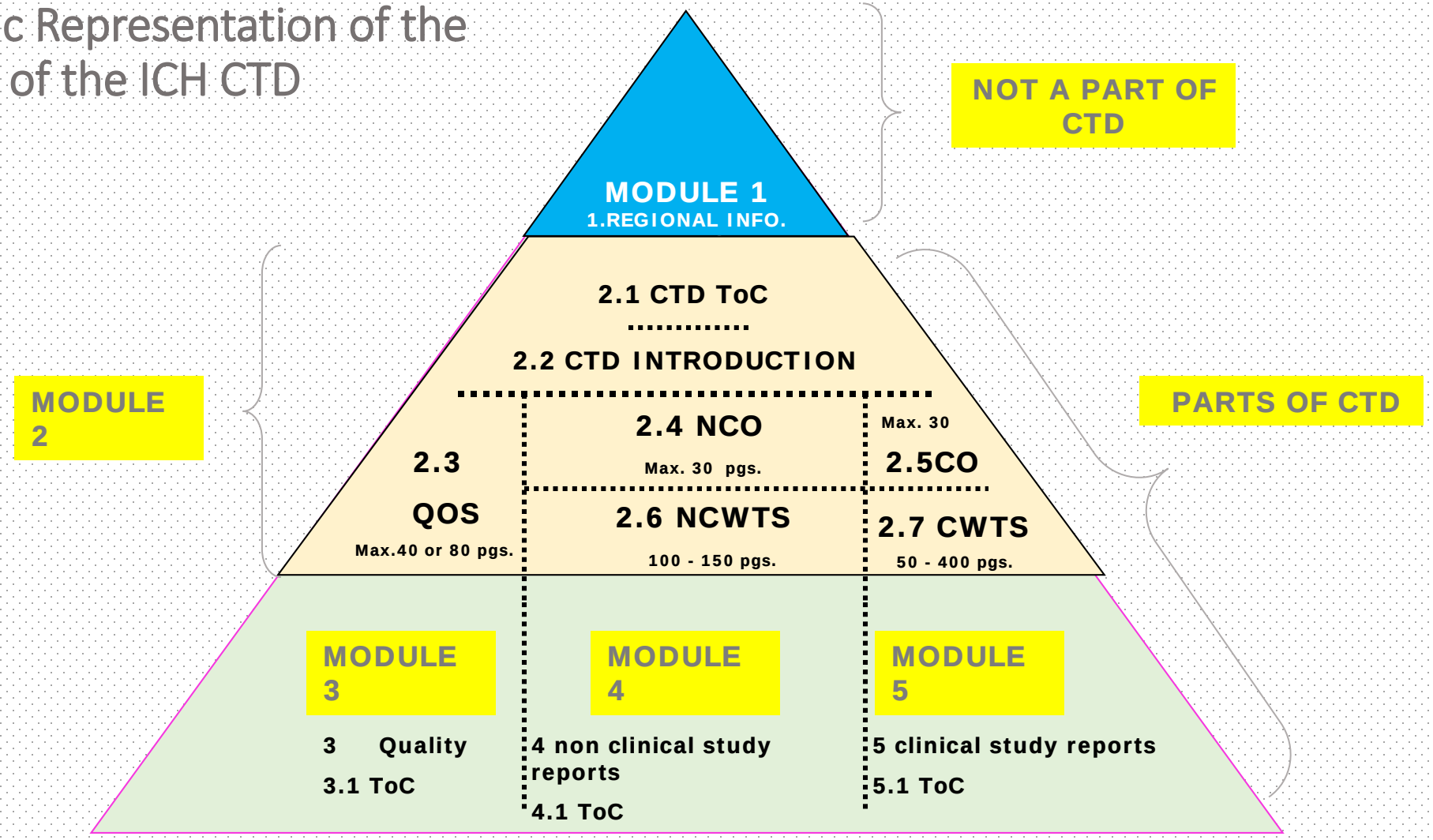
Control Strategy

Quality be Design

- **Continuous improvement is a hallmark of quality by design**
- **G. Taguchi on Robust Design: design changes during manufacture can result in the last product produced being different from the first product**
- **In pharmaceutical manufacturing, we do want this :**
  patients and physicians must count on each batch of drug working just like the batches that came before

Consistency Consistency Consistency

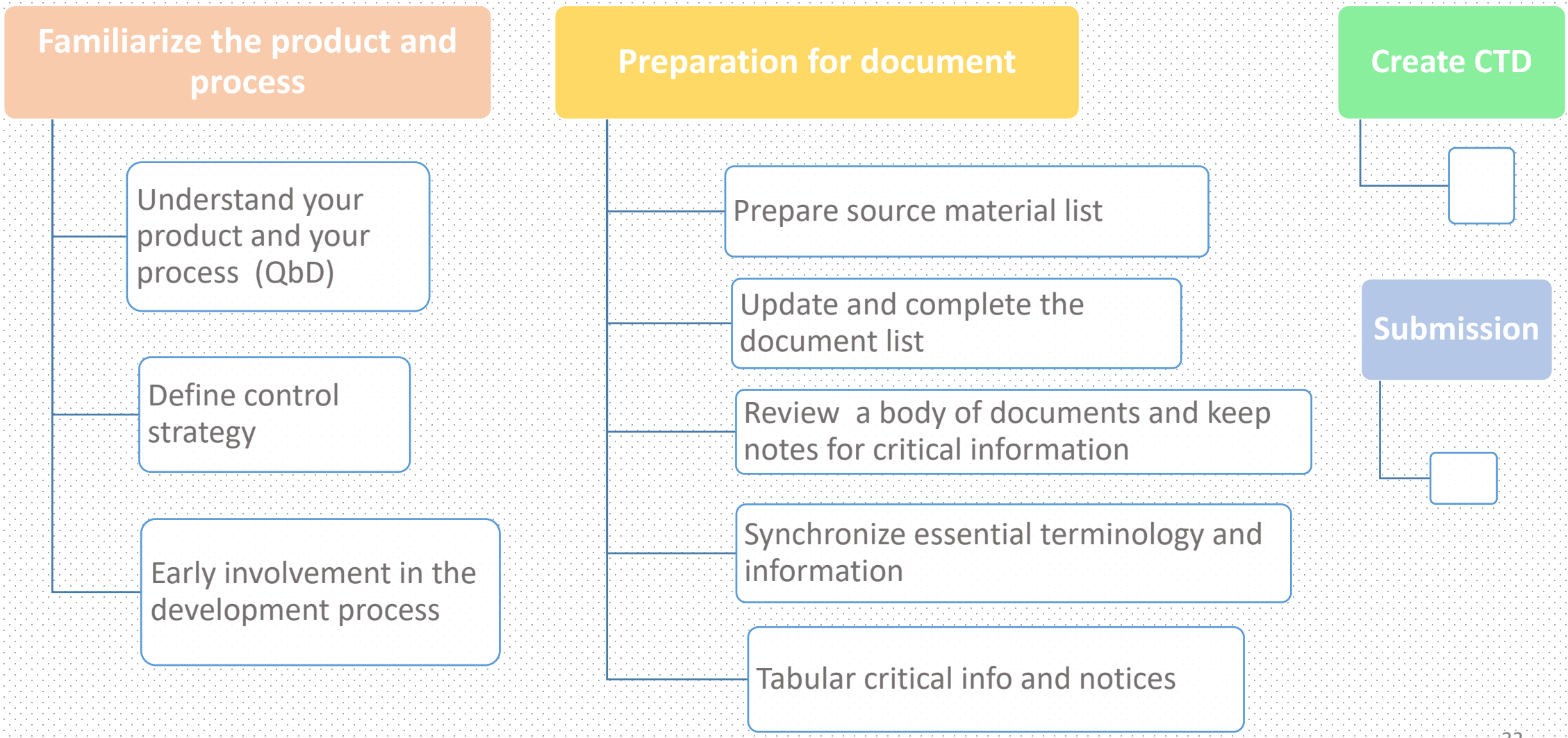
Diagrammatic Representation of the Organization of the ICH CTD



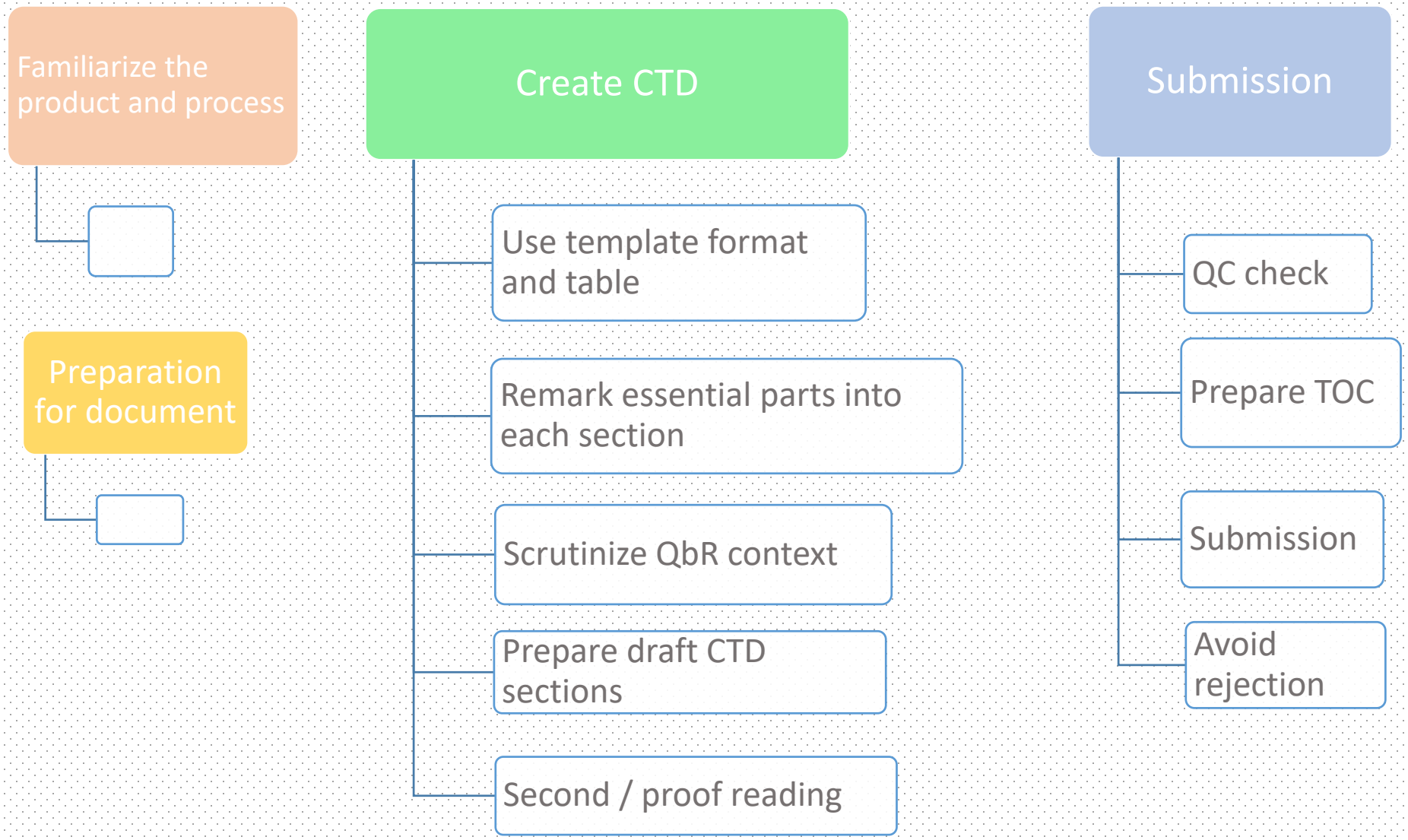
NDA vs., ANDA Review Process

NDA requirement	ANDA requirement
1. Labeling	1. Labeling
2. Pharm/Tox	
3. Chemistry	2. Chemistry
4. Manufacturing	3. Manufacturing
5. Controls	4. Controls
6. Inspection	5. Microbiology
7. Testing	6. Inspection
	7. Testing
8. Animal Studies	
9. Clinical Studies	8. Bioequivalence
10. Bioavailability	

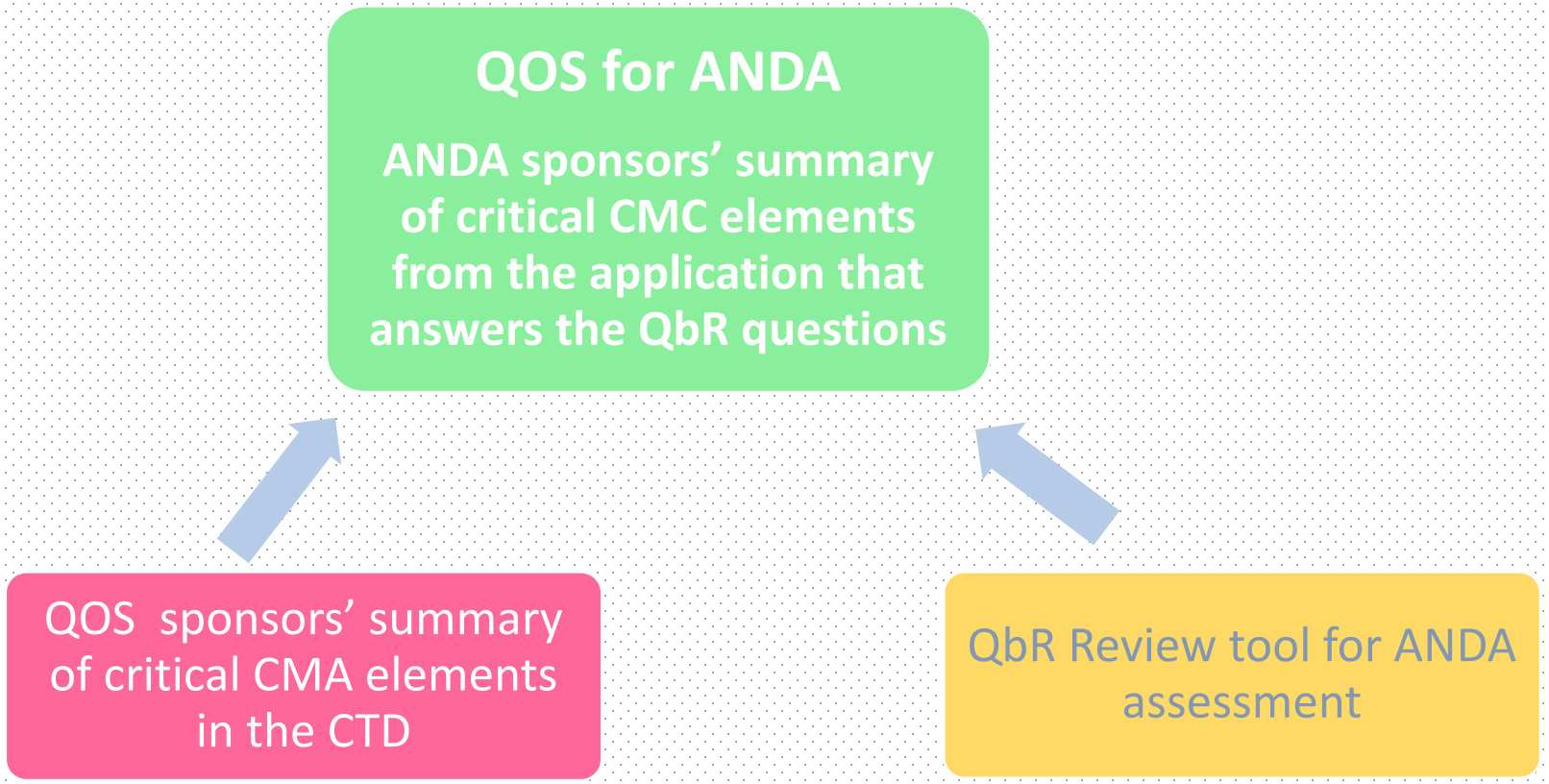
Tips for CTD preparation (1/2)



Tips for CTD preparation (2/2)



QbR – QOS for ANDAs



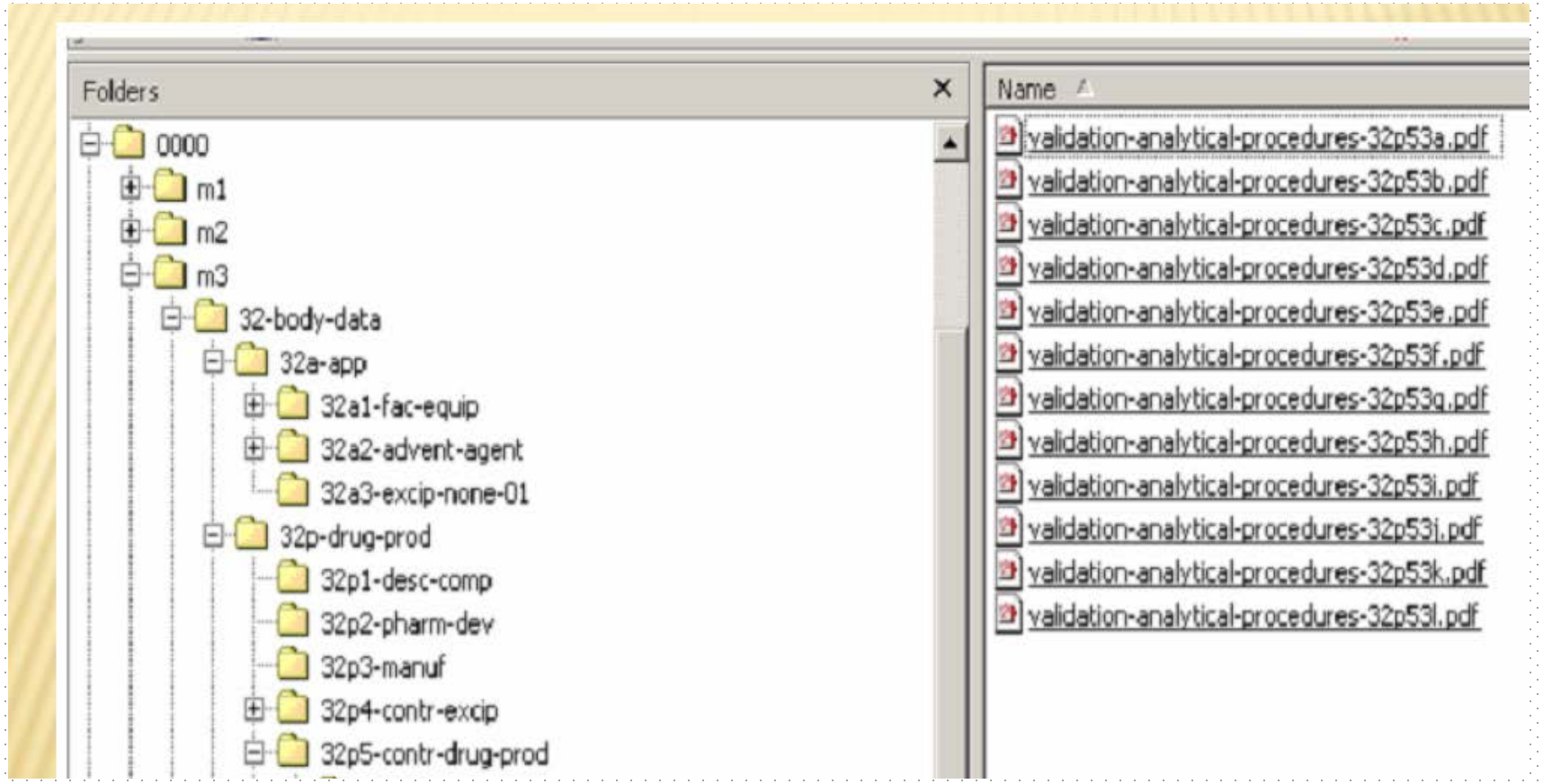
QbR Example

Q: What are the unit operations in the drug product manufacturing process?

A:

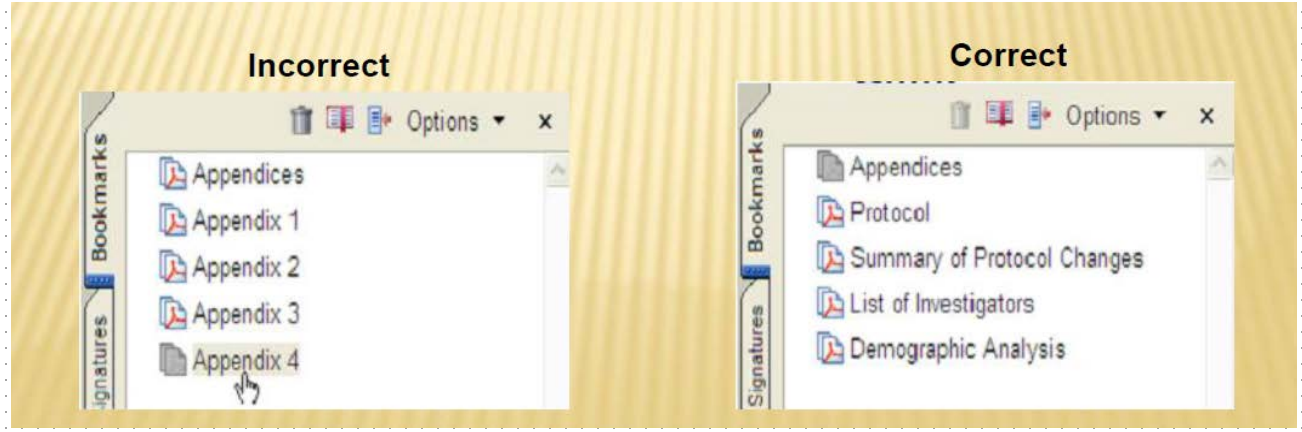
- Detailed flow chart
  - Unit operations (blending, drying, etc.)
  - Equipment
  - Point of material entry
  - Identification of critical steps (with process or other controls)
- Narrative summary of the manufacturing process
- Reprocessing/reworking statement
- Executed batch record and blank product batch record

Document Granularity – Module 3 example



Bookmarks and Hyperlink

- Bookmarks
  - Match the document TOC
  - Bookmarks – up to Level 4, e.g., 1.1.1.1
  - For documents with multiple granules, each granule has its own bookmarks
  - Provide Bookmarks with Intuitive names



QC of eCTD

Precompilation

- QC interdocument links
- 100% QC that all bookmarks and hyperlinks are live
- 100% QC that all bookmarks and hyperlinks point to the correct targets
- Check all the documents for presence and location
- Check document titles in eCTD viewer

Postcompilation

- Validate eCTD
- Recheck for broken links

Project management

Project management

- Earlier time essence
- Team-up
- Project management tool
- Source material list
- Task work / responsible table
- Document matrix

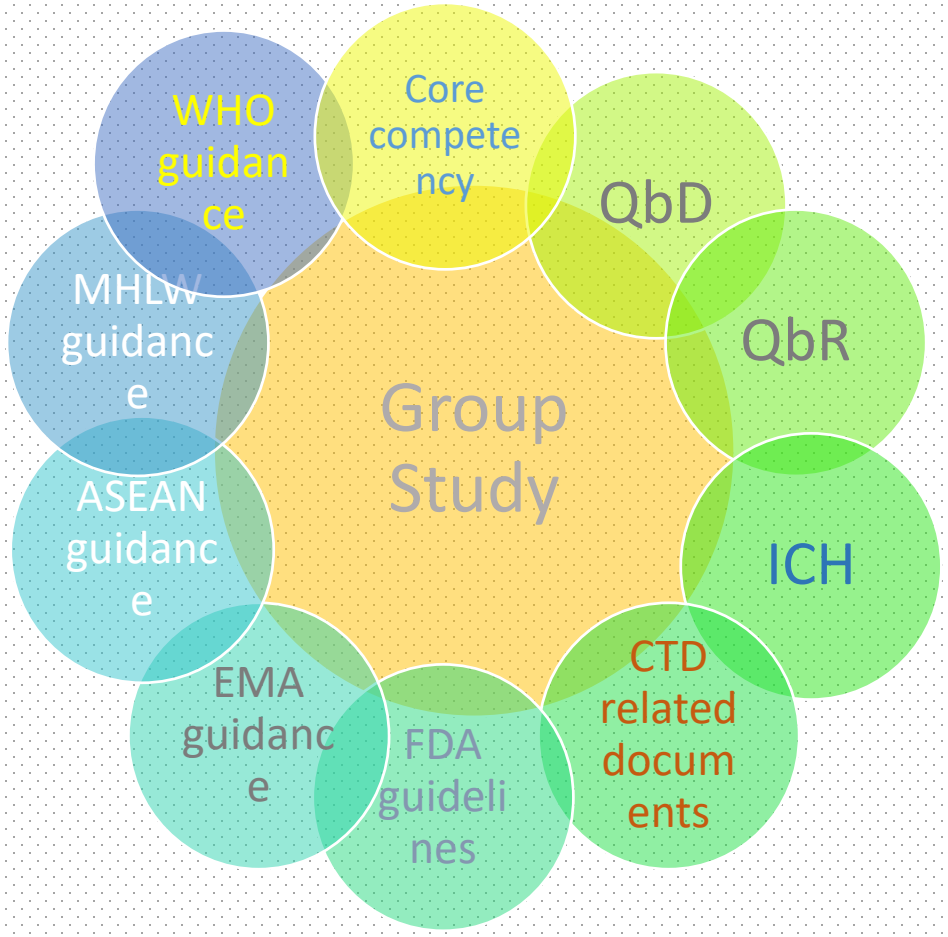
Quality management

- Consistency of submission package
- Template / format / table / figure
- Preparation and review process
- Secondary review / proof reading
- TOC / Cross reference
- QC check

Communication

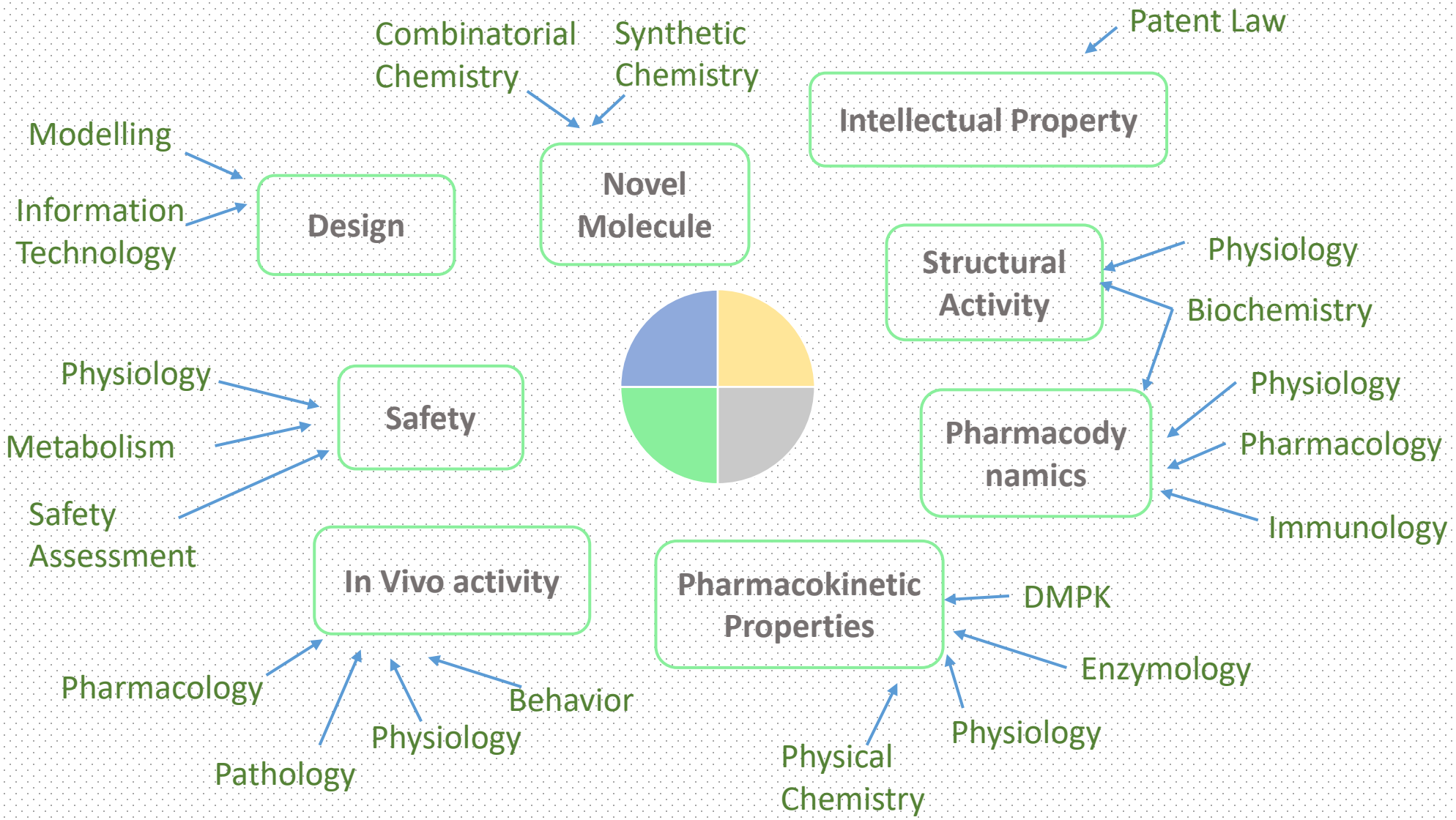
Meeting	Inquiry/Request	Response	Contact point
• Pre-sub meeting • Post-sub meeting • Clear defined question • Well-prepared documents • Scientific rationale • Meeting minutes • Follow-up	• Completeness • Additional information • Clarification of question • Consultation meeting • Regulatory Strategy • Timeline • Response package	• Regulatory strategy • Timeline • Project management tool • Response package : careful review	• Professional knowledge • Detailed management skill • Scrutiny Timeline • Communication skill • Effectiveness and efficiency

Training program



- Strengthen your core competency to application
- Keep update current regulation Guidances
- Prepare common error bug checklist
- Sharing knowledge and experience
- Readership writing skill
- Story telling skill
- Quality Culture
- Data security
- Hard and soft skill

Drug Discovery –Convergence of Disciplines



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Thank You For Your Attention