Lecture # 8
Scale-up, Process validation, Post Approval Changes, and LCM Initiatives (Drug Product)

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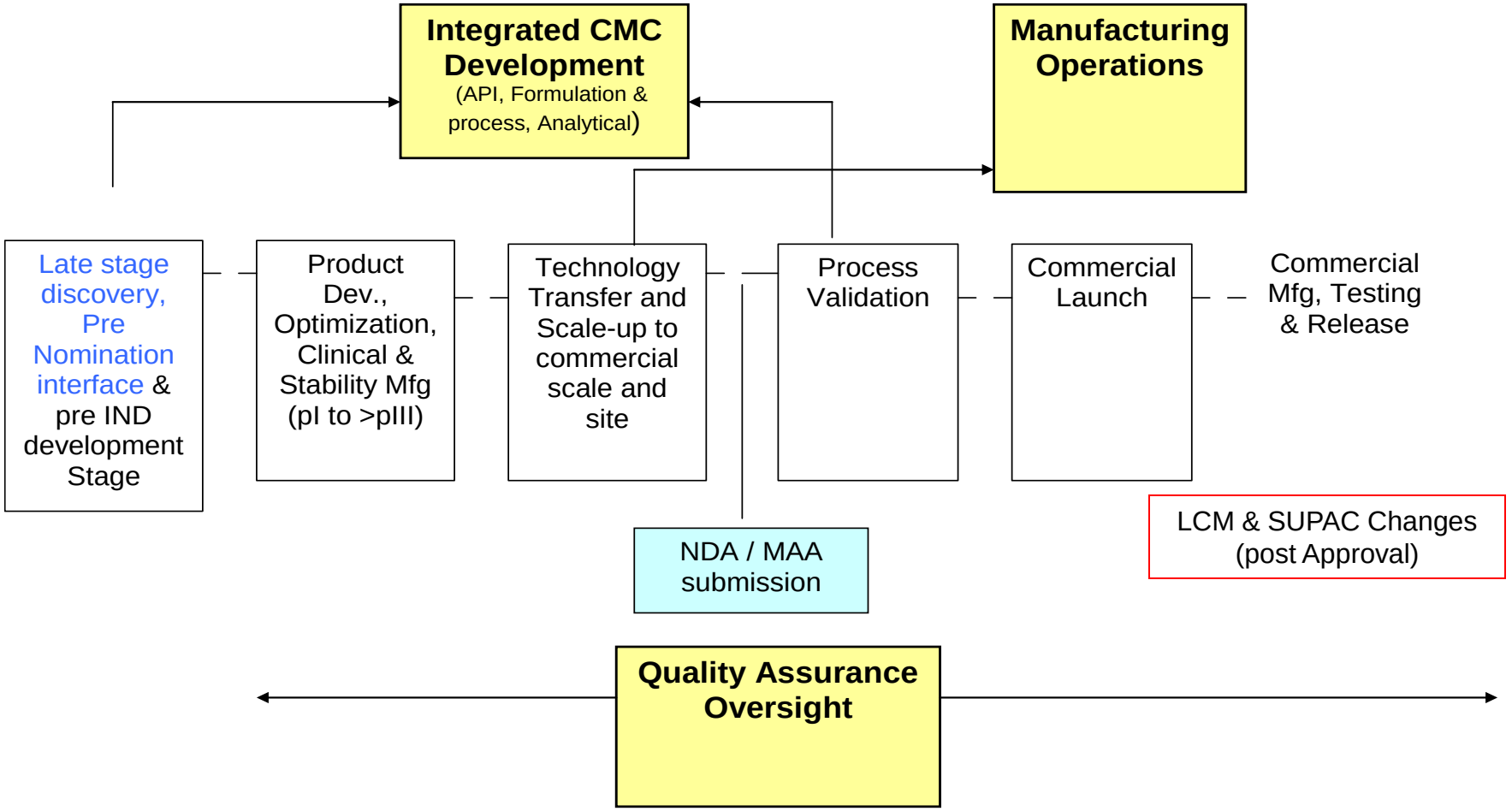
Lecture Outline

1. Scale-up
2. Pre Approval Inspections
3. Process Validation
4. Statistical Process Capability (Cpk)
5. Post Approval Changes
6. Life Cycle Mgmt (LCM) Initiatives
7. References

Recall: CMC Life Cycle Approach
Candidate Nomination to Commercialization



1. Scale-up & Technology Transfer

- Increase in batch size resulting:
  - Increased throughput
  - Reduced cost of goods
  - Commercially viable

- Given most pharmaceutical process are batch processes:
  - Keep operating principle of equipment constant
  - Keep geometry constant
  - Process time more or less kept constant

- Unchanged product quality

- Commercial scale-up is usually not > 10 fold as that of pilot scale.

Scale-up & Technology Transfer

- Technology Transfer = "Transfer of Knowledge"
- Scale-up: Increase in batch size resulting 'unchanged product quality"
  - ↑ throughput, ↓ COGs, Commercially Viable

Input Needs

Facility and Equipment Qualification

Pilot scale process optimized and robustness established

Documentation
MBRs, **Scale-up protocol**, Test methods, DP specifications

Strategize Plans

1. X number of batches; difficult for DOE
2. Develop scale-up strategy
3. Scale-up factors
4. Before submission (preferred)

Output Deliverables

Process scaled up to commercial scale & site

Proposed MBR in NDA

Scale-up report issued

Establish basis for Process validation

2. PAI Preparation

- Expected within 4-10 months of filing
- Multi fold objectives:
  - Mfg site & quality systems are ready
  - Product is ready
  - Review key development documents
- PAI preparation is a process…….not an event
- Preparation Starts before phase III batches
- Ensure all development issues are identified and covered
  - Product Development Report
  - Process Validation Protocol

- PAI Process:
  - Create a PAI Team:
  - QA lead, CMC co lead, SMEs
  - Opening presentation (product & site) – 10 slides)
  - Develop Checklist and gap analysis:
    - List of all batches with disposition status
    - Failed batches
    - Deviations and Investigations
    - OOS and OOTs
    - Method Validation & Transfers
    - Primary stability
    - Pivotal batch records vs proposed commercial
    - Verification of supplier CoA
    - Many more……
  - Development holes and resolutions
  - Weekly meetings – internal and with CMOs
  - PAI mock inspections
  - Master the art of Managing CMOs remotely

3. Process Validation

- Process Validation is establishing documented evidence which provided high degree of assurance that a specific process will consistently produce a product meeting its predetermined specification and quality attributes.
- Culmination of Product Development efforts
  - Confirmation of PD cycle
- 3 successive, successful batches (historically, 1987 Guideline)
- New Guidance issued recently in 2011
- No development during process validation
- Documented via process validation protocols and reports
- Success can be proven by statistical or empirical means
- Process validation is usually undertaken after NDA submission.
  - May be before / or after NDA approval
  - Can be before / or after PAI
  - Can be used for commercial distribution

Why Validate

Business Practices

- Common sense mandates it !
- GMP regulations require it !
- Good business practice:
  - Value of early detection
  - Reduction in quality failures
  - Reduction in utility costs
  - Capital savings / increased throughput
  - Reduced testing
  - Increased knowledge
  - Better management programs
  - More rapid start up – new equipment & facilities
  - Better maintenance programs
  - Better adherence to procedures
  - Reduced liability !

Regulatory & Compliance Expectations

- GMP regulations require it
- 21 CFR 211, 21CFR 820
- 211.68: Automatic, mechanical, and electrical equipment
- Subpart F: Production & Process Controls
  - 211.100: Written procedures; deviations
  - 211.110: Sampling & testing of in-process materials and drug products
  - 211.113: Control of microbiological contamination
- 211.84: Validation of suppliers, component testing, conatiner0closure, test results….
- Guide to inspection of Bulk Pharmaceutical Chemicals, p 19 & 20
- Pre-Approval Inspections – 7346.832:
  - Equipment qualification, cleaning validation, methods validation, process validation
- Process validation Guideline, 1987
- Process Validation Guidance, 2011

Process Validation

Process Validation: Establishing documented evidence providing high degree of assurance that a specific process will consistently produce a product meeting its predetermined specification and quality attributes (1987)

Input Needs

Facility and Equipment Qualification

Process Scale-up & robustness

MBRs, Test Methods, Specs

Process Validation protocol
Master validation Plan
Site Validation Plan

↓

Will be needed at PAI

Strategize Plans

1. In essence 3 successive successful batches at commercial scale
2. No experimentation
3. After submission and before commercial distribution (mandatory

Output Deliverables

3 batches Mfd & Released
- All pre established criteria met
- Deviations have no impact

Process Val Report issued

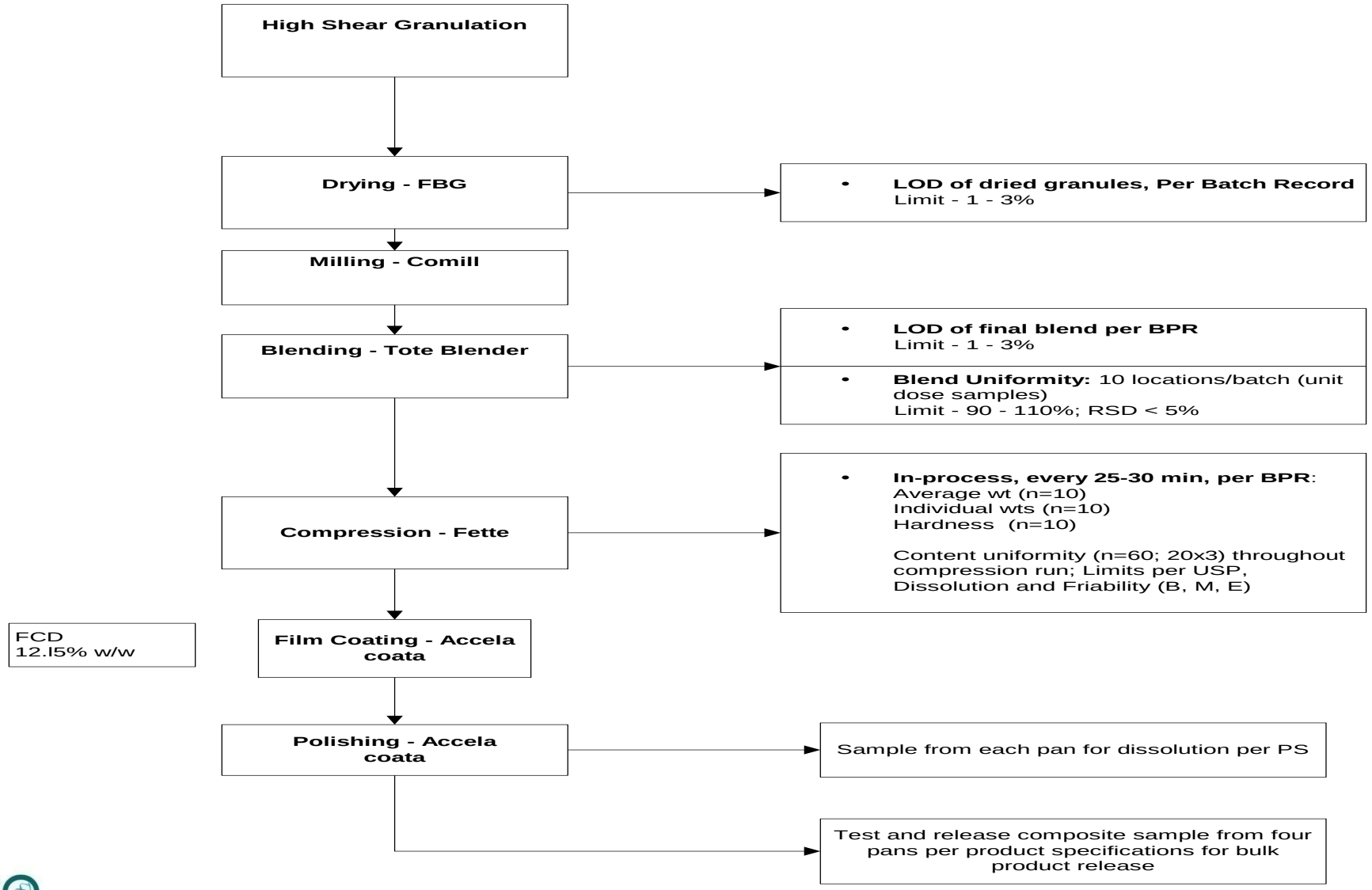
Batches can be sold

US: Neither required to be complete at submission nor at PAI
EU: Expect a question on providing PV sumamry at Day 120

Outline for Process Validation Protocol

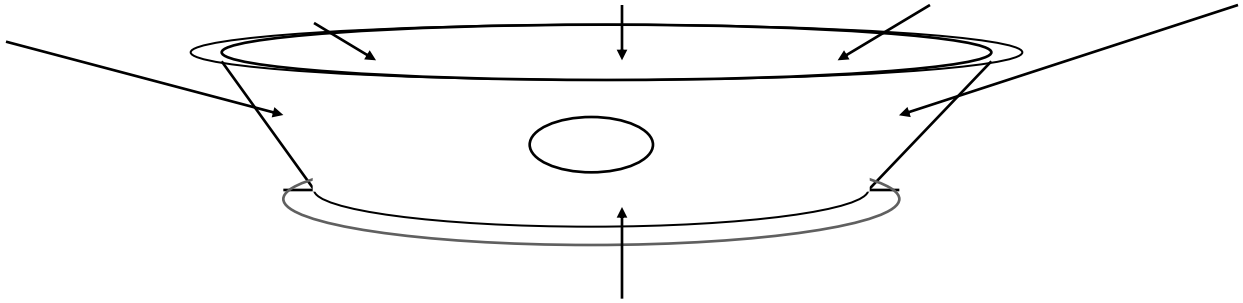
- Review & Approval
- Objective & Scope
- Overview
- Formulation Composition
- Manufacturing Process Description & IPCs
- Sampling Plan:
  - Process steps to be sampled, sampling equipment, sampling quantity, sample containers, sampling interval, sampling locations, labeling, who samples….
- Sampling Diagrams
- Testing:
  - Specify labs testing, analytical procedures
- Acceptance Criteria:
  - For each critical step, analysis within & between batches, statistical methods to be bused….
- Appendices:
  - Copies of MPRs, Product Spec, IQ/OQ approval, Dev Report..
- Amendment & Addendums

Sampling & Testing Plan for Process Validation



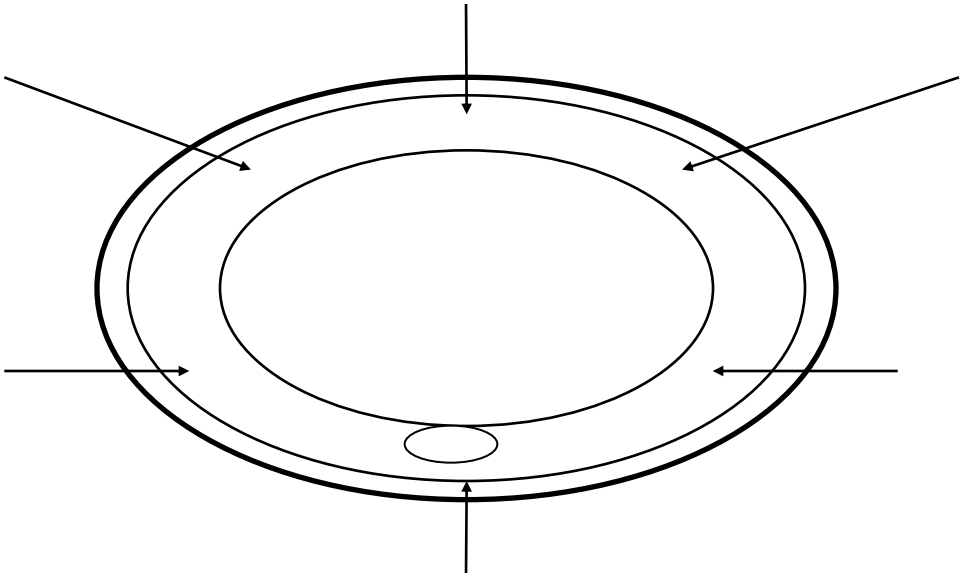
Sampling Diagram for Glatt Fluid Bed Granulator / Dryer

Front View

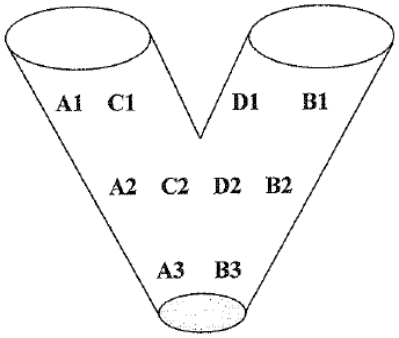


5-6 samples through out the product bowl

Top View



V Blender

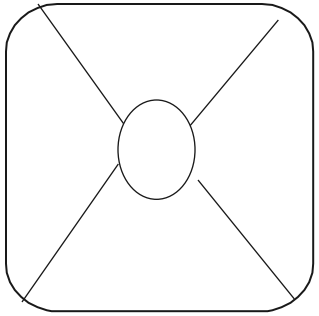


- Sample: 10 location
- Unit dose samples (1-3X of Tablet / capsule fill weight)
- Sample using a theif equipped with a suitable chamber size
- Test the entire sample; don't sub sample

Sample Site 2
Top = 2T
Middle = 2M
Bottom = 2B

Conical bottom tote blender top view sample sites

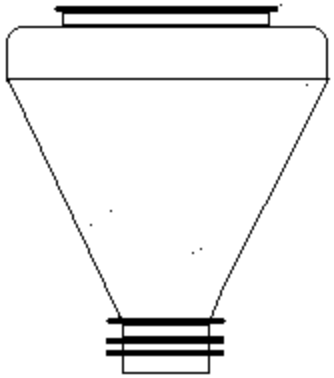
Sample Site 1
Top = 1T
Middle = 1M
Bottom = 1B



Sample Site 3
Top = 3T
Middle = 3M
Bottom = 3B

Sample Site 4
Top = 4T
Middle = 4M
Bottom = 4B

Sample Site 1
Top = 1T
Middle = 1M
Bottom = 1B



Sample Site 3
Top = 3T
Middle = 3M
Bottom = 3B

Conical bottom tote blender front view sample site

Acceptance Criteria for Blend Uniformity

- Becomes easy, if you can meet
  - Blend uniformity, n=10:
    - Sample locations throughout the blender
    - Unit dose sample weight (1-3X)
    - Individuals: within ± 10% of mean (absolute)
    - RSD (related std deviation): ≤ 5.0%
  - Content uniformity of core tables / capsules:
    - Take 20 samples throughout compression run
    - 3T/sample X 20 samples = 60 samples
    - Individuals: 75.0% -125%
    - Location Mean (from each sample):90.0% -110.0%
    - RSD (related std deviation): ≤ 4.0% :

Process Validation – 2011 Guideline

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070336.pdf

- New guideline (2011) – replaces the 1987 guideline
- Key Premise
  - Quality, safety, and efficacy are designed or built into the product.
  - Quality cannot be adequately assured merely by in-process and finished-product inspection or testing.
  - Each step of a manufacturing process is controlled to assure that the finished product meets all quality attributes including specifications.
- 3 stages to PV:
  - Stage 1: Process Design
  - Stage 2: Process Qualification
  - Stage 3: Continuous Process verification
- No longer necessary for 3 successive successful:
  - Up to sponsor to justify # of batches
- What should be # of batches?
  - Depends
  - Formulation & Mfg process complexity
  - Risk Assessment
- PT Article (Feb 2011):
  - 1 batch:
    - Simple change, IR products
    - Low volume products (< 5 batches /yr)
  - 3 batches:
    - IR solid dosage with > 10% DL
    - Non sterile or sterile with > 10 % DL
    - Oral or injectable solutions – aq or solvent
  - 5 batches:
    - IR solid dosage with < 1-10 % DL
    - Sterile solids with < 1-10 % DL
    - Oral, topical or injectable gels in aq or solvent bases
  - 7 batches (excessive ?):
    - IR solid dosage with < 1 % DL
    - Sterile solids with < 1 % DL
    - Oral, topical or injectable suspensions, creams, ointments, suppositories
  - 9 batches (???): Mod Release (MR)

PV guideline – Glossary

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070336.pdf

- **Capability of a process: Ability of a process to produce a product that will fulfill the requirements of that product. The concept of process capability can also be defined in statistical terms. (ISO 9000:2005)**
- **Commercial manufacturing process: The manufacturing process resulting in commercial product (i.e., drug that is marketed, distributed, and sold or intended to be sold). For the purposes of this guidance, the term commercial manufacturing process does not include clinical trial or treatment IND material.**
- **Concurrent release: Releasing for distribution a lot of finished product, manufactured following a qualification protocol, that meets the lot release criteria established in the protocol, but before the entire study protocol has been executed.**
- **Continued process verification: Assuring that during routine production the process remains in a state of control.**
- **Performance indicators: Measurable values used to quantify quality objectives to reflect the performance of an organization, process or system, also known as performance metrics in some regions. (ICH Q10)**
- **Process design: Defining the commercial manufacturing process based on knowledge gained through development and scale-up activities.**
- **Process qualification: Confirming that the manufacturing process as designed is capable of reproducible commercial manufacturing.**
- **Process validation: The collection and evaluation of data, from the process design stage through commercial production, which establishes scientific evidence that a process is capable of consistently delivering quality products.**

4.Statistical Process Capability

- Historical Perspectives
- Why ??? !!!!
- Assumptions
- Terminologies, computational methods
- Interpretation and Usage
- Broad Applications

Historical Perspectives (SPC and Process Capability)

- Statistical process control (Schewart)
- Japanese Industry – Deming / Tagunchi…
- Motorola: 1983 National Quality Award
- Ford Motor Company, 1986
- Pharmaceutical literature, applications…

Why Process Capability?

- Provides a means for common and easily understood language for quantifying the performance of manufacturing process.
- Quantification of process location (mean) and variation (standard deviation) is central to product quality.
- Process capability provides a means to compute unitless indices (PCIs) using process location and variation relative to pre-established specifications (target & limits).
- Provides a measure for “High Degree of Assurance,” a key requirement for process validation.

Assumptions

- The process is in a state of statistical control.
- The data are normally distributed.
- The data collected are collected from independent random samples.
- The data are truly representative of the process.

Summary of PCIs – 1st Generation

Index	Term	Equation	Usage
C_p	*Potential Capability*	$\frac{USL - LSL}{6\sigma}$	process potential for two-sided specification limits
C_{PU}	*Upper Capability Index*	$\frac{USL - \mu}{3\sigma}$	process performance relative to upper specification limit
C_{PL}	*Lower Capability Index*	$\frac{\mu - LSL}{3\sigma}$	process performance relative to lower specification limit
K	*Non-centering Correction*	$\frac{2\lvert m - \mu \rvert}{USL - LSL}$	deviation of process mean from midpoint (m) of specification limits
C_{pk}	*Demonstrated Excellence*	$Min\ \{ C_{PL}, C_{PU}\}$ $= C_p(1 - k)$	process performance for two-sided specification limits

Interpretation

Approximately Normal	Exact Normal
$\mu \pm \sigma$ contains approximately 68% of the measurements.	68.26%
$\mu \pm 2\sigma$ contains approximately 95% of the measurements.	95.44%
$\mu \pm 3\sigma$ contains almost all of the measurements.	99.73%

Potential Capability - C_p (V. Kane); Using a $\pm$ 3σ spread, for a process with normal distribution:

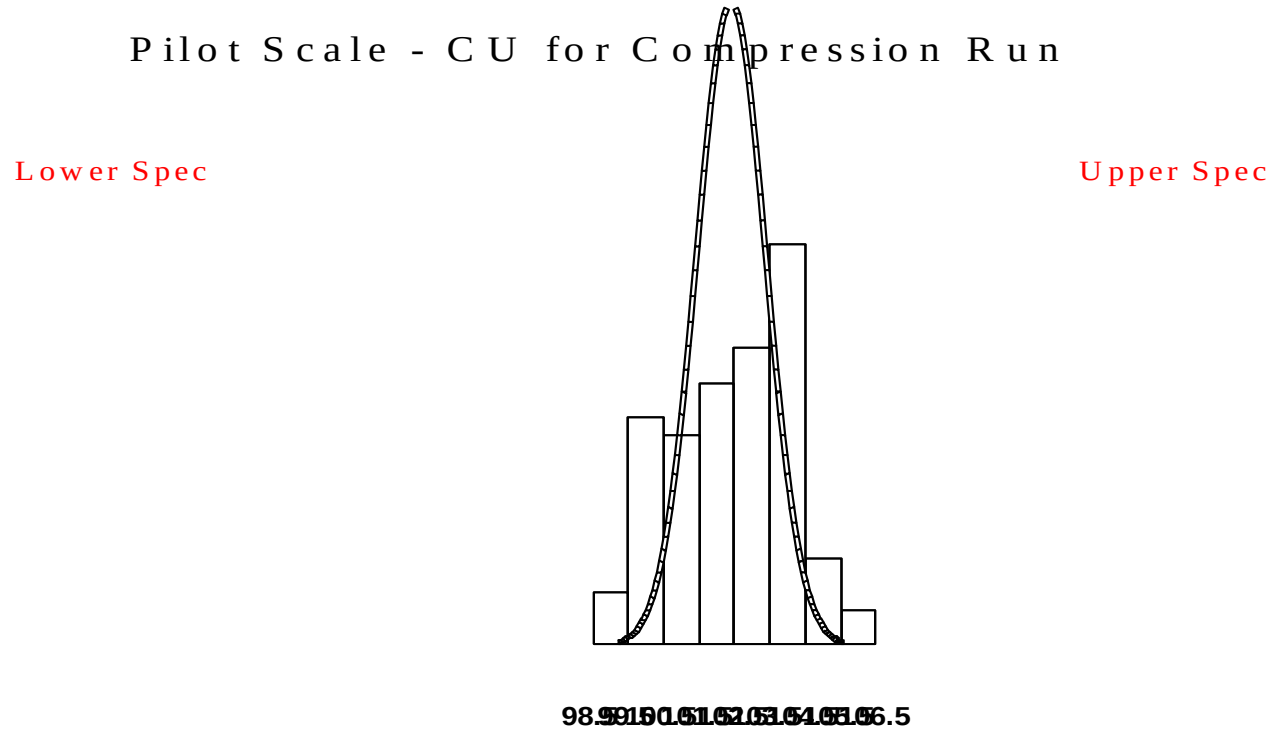
C_p=1.0 means 0.27% of parts are beyond specification limits.
C_p=1.33 means 0.007% of parts are beyond specification limits.

To consistently achieve a C_{pk} of 1.33 during routine production, C_{pk} > 1.33 should be obtained in validation.

Case Study
Quantify process performance in PD cycle

- NDA Product; B.S: 15.0 Kg & 120 kg.
- Drug Loading: 6.7%; Compression Stage.
- Pilot: 3 batches; 5 samples; 6T/sample (n=90)
  Commercial: 4 batches; 10 spls; 3T/spl (n=120).
- Apply Process Capability for 85-115 % CU limits for pilot scale & commercial scales.

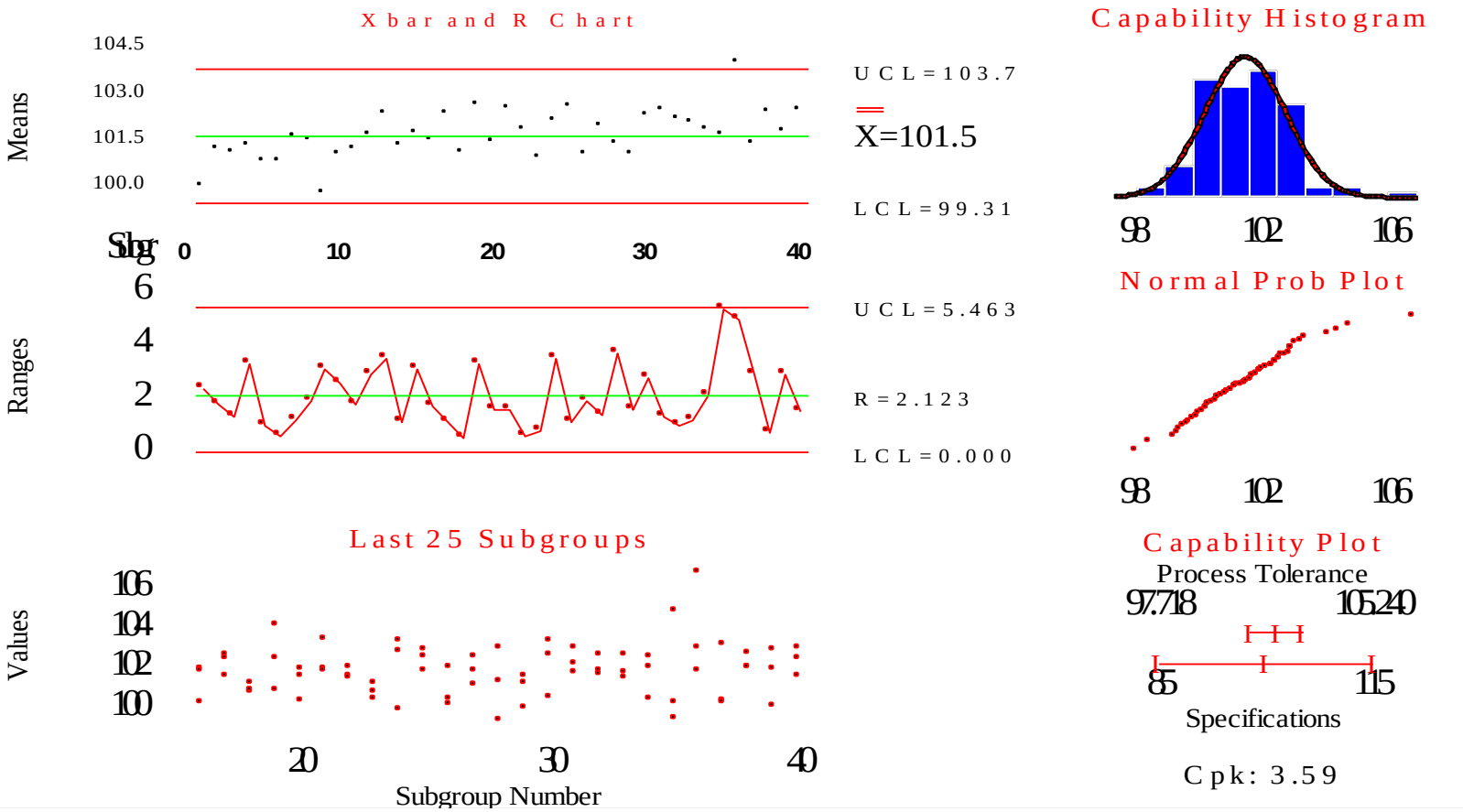
Process Capability - Pilot Scale



Cp	5.11	Targ	100.000	Mean	102.393	%>USL Exp	0.00	PPM>USL Exp	0
CPU	4.30	USL	115.000	Mean+3s	105.327	Obs	0.00	Obs	0
CPL	5.93	LSL	85.000	Mean-3s	99.459	%<LSL Exp	0.00	PPM<LSL Exp	0
Cpk	4.30	k	0.160	s	0.978	Obs	0.00	Obs	0
Cpm	1.68	n	90.000						

MINITAB Six Pack- Commercial Scale

Commercial Scale - CU for Compression Run



5. Scale-up & Post Approval Changes (SUPAC)

Scale-up issues prior to 1990s

- FDA guideline 22-90:
  - Biobatch size to be greater than 10 % or 100,000 units (which ever is greater)
- Issues:
  - Did not specify same equipment or even similar equipment
- Failed to allow for:
  - Formulation ranges
  - Increased efficiency of larger batch sizes
  - Manufacturing process & equipment changes
  - Scale-up changes
- FDA & University of Maryland contract:
  - Early 1990s

Post 1990s:

- Several PAC Guidances
  - SUCPAC-IR, SUAPC-MR (1990s)
  - Equipment Addendum for SUAPC IR and SUAPC MR
  - PAC guidance (2004)
  - Draft guidance; ~ 40 AR changes (2010)
- Drug Product (DP) SUPAC changes:
  - Product formulation composition
  - Manufacturing process / equipment
  - Component sources / specifications
  - Product specifications & analytical methodology
  - Packaging materials / suppliers / specs
  - Manufacturing, packaging & testing sites
- Type of Change vs. Submission
  - Major Change – PAS (4-6 months review)
  - Moderate Change CBE 30 or CBE 30
  - Minor Change – Annual Report (no approval)
  - Level of change –I, II, III

Overview of PAC Guidance
Changes to an Approved NDA/ANDA

- Objective:
  - Provide recommendations to holders of NDA/ANDA intending to make post approval changes.

- Scope:
  - To the extent that the reporting categories in this Guidance are inconsistent with previous Guidances, the recommended reporting categories in prior Guidances (i.e.: SUPAC) will be superceded by this Guidance

  - This guidance does not provide extensive recommendations on composition or components; so follow SUPAC for these type of changes.

- Summary contents:
  - Types of changes (8)
  - Reporting Categories (4):
    - PAS, CBE 30, CBE, AR

PAC for NDA/ANDA Overview (Cont'd)

- Types of Changes (8)
  - Components and Composition, Manufacturing Sites, Manufacturing Process, Specifications, Package, Labeling, Miscellaneous Changes, Multiple Related Changes

- Reporting Categories (4):
  - Major Change (PAS):
    - Has substantial potential to effect on identity, strength, quality, purity, or potency of product as related to safety or efficacy.
    - Would required Prior Approval Supplement (PAS)
    - FDA Approval is required prior to distribution of product made using the change
  - Moderate Change (CBE and CBE 30):
    - Has moderate potential to effect on identity, strength, quality, purity, or potency of product as related to safety or efficacy. Two types of moderate change:
      - Supplement - Changes Being Effected 30 Days (CBE 30): The product made using the change can be distributed 30 days after FDA's receipt of supplement, if acceptable and complete.
      - Supplement – Changes Being Effected: Product made using the change can be distributed upon FDA's receipt of supplement.
  - Minor Change (AR):
    - Has minimal potential effect on identity, strength, quality, purity, or potency of product as related to safety or efficacy.
    - Describe these minor changes in "annual report"

Level 3 changes for IR product - Summary

Change	Level	Filing	Test Documentation	Invitro Disso	In vivo BE
Mfg Site Change	3 (different campus)	CBE	•Location of new site & updated batch records (CBE) •Application release requirements •3 batches with 3M accelerated stability (CBE); 3 batches on long term stability (AR)	Case B (multi point dissolution in application medium)	None
Batch size	2 (beyond 10X of pilot or bio batch)	CBE	•Application release requirements • 1 batch: 3 M accelerated stability (CBE) •1 batch on long term stability (AR) •Notify change; updated batch records (AR)	Case B	None
Mfg Equipment	2 (different design, operating principle)	PAS	•Location of new site & updated batch records •Application release requirements •3 batches with 3M accelerated stability (CBE); 3 batches on long term stability (AR)	Case C (multi point and multi media)	None
Mfg Process	2 (parameters outside NDA/PV)	CBE	•Application release requirements • 1 batch on long term stability (AR) •Notify change; updated batch records (AR)	Case B	None
Mfg Process	3 (wet granulation to Dry blending)	**PAS**	•Location of new site & updated batch records (CBE) •Application release requirements •3 batches with 3M accelerated stability (CBE); 3 batches on long term stability (AR)	Case B	In vivo BE or waiver justification

Additional Examples

Change	IR / MR	BCS	Type of Change / Submission	Studies
Mfg Site Change	MR	N/A	Major - PAS	Single dose BE study, ICH stability, BR from new site
Mfg Site Change	IR	Class I	Major - PAS	No BE, multi point dissolution (f2), ICH stability, BR from new site
Wet Granulation to Direct Blending	IR	N/A	Major - PAS	Case b dissolution, in vivo BE (or backed by IVIVC), ICH stability
Change in operating principle for equipment	IR / MR	N/A	Major - PAS	In vivo BE: None Disso: Case C Stability:
Manual to automated or alternate equipment of same design	IR	N/A	Minor – Annual Report	In vivo BE: None Disso: none beyond application 1 batch on long term stability

Guidances are fairly clear

Case Study I - MR Product

prior approval change

- Case Description
  - Modified Release Tablets, > 50 % drug loading
  - Change in supply chain:
    - Between 1st and 2nd pivotal efficacy studies (API and D)
    - Between 2nd pivotal efficacy and TBM (only API vendor change)
  - DP Mfg:
    - 120 Kg for 2nd pivotal efficacy
    - 500 Kg for commercial scale.
  - Changes before NDA filing
  - IVIVC failed

- Question
  - How do we propose to do “bridge CMC changes”?

- Special note
  - Not typical SUPAC changes
  - Changes occurring before filing; but can apply spirit of SUPAC

Case Study I (Cont'd):

- What are the changes ?
  - Change in API vendor, Change in DP batch size, Impact of API change on DP performance
- Good part:
  - Mfg process for DP same between 120 kg and 600 Kg, product specifications tightened.
  - Formulation of DP is identical
- Proposed strategy for bridging:
  - ✓ demonstrated physico - chemical equivalency of API between old and new CMO
  - ✓ process development studies for DP using new API to ensure all in-process controls are met and product specs are met (4 lots……not just 1 lot)
  - ✓ primary stability studies for new API and for DP (120 Kg scale) made with this new API – 3 batches – per ICH. Propose to submit NDA with 6M 40C/75 RH, 12M 25C/60 RH and commitment for long term ambient stability.
  - ✓ complete commercial scale-up studies (500 Kg), while stability studies are ongoing, prior to NDA submission
  - ✓ Completed BE studies for DP (DP in pIII vs DP in PS (120 Kg) – considered pivotal BE:
    - ✓ Highly variable drug: required replicated design for BE study
  - ✓ In vitro dissolution similarity, between DP at 120 and 500 Kg scales, in different pH media
  - ✓ Summarized all bridging studies along with BE study in PD report
  - ✓ Executed batch records from pivotal BE (120 Kg) and proposed batch records (500 Kg) from commercial scale in NDA

Post Approval Changes in EU

- Called Variations
  - Procedure Type 1A, 1B, II
- Scope for Quality Changes:
  - Active Substance:
    - Manufacture, control of active substance, container-closure, stability, design space
  - Finished Product :
    - Description and composition, manufacture, control of excipients, control of finished product, container-closure, stability, design space
- Tables for changes
  - Type of change, conditions to be fulfilled, documentation to be supplied, procedure Type
- Classification Guideline (pdf and MS word)
  - http://ec.europa.eu/health/files/betterreg/pharmacos/classification_guideline_adopted.pdf

Variation requirements in EU

B.II.b: Manufacturing (Mfg Process) - Relevant

B.II.b.3: Change in the manufacturing process of the finished product	Conditions to be fulfilled	Documentation to be supplied	Procedure Type
a) Minor change in the manufacturing process of an immediate release solid oral dosage form or oral solutions.	1, 2, 3, 4, 5, 6, 7	1, 3, 4, 6, 7, 8	IA
b) Substantial changes to a manufacturing process that may have a significant impact on the quality, safety and efficacy of the medicinal product			II
c) The product is a biological/immunological medicinal product and the change requires an assessment of comparability.			II
d) Introduction of a non-standard terminal sterilisation method			II
e) Introduction or increase in the overage that is used for the active substance			II
f) Minor change in the manufacturing process of an aqueous oral suspension.		1, 2, 4, 6, 7, 8	IB

Conditions (projected to be Yes to all)

1.	No change in qualitative and quantitative impurity profile or in physico-chemical properties. (Yes)
2.	The product concerned is not a biological /immunological or herbal medicinal product. (Yes)
3.	The manufacturing principle including the single manufacturing steps remain the same, e.g. processing intermediates and there are no changes to any manufacturing solvent used in the process. (Yes)
4	The currently registered process has to be controlled by relevant in-process controls and no changes (widening or deletion of limits) are required to these controls. (Yes)
5.	The specifications of the finished product or intermediates are unchanged. (Yes)
6.	The new process must lead to an identical product regarding all aspects of quality, safety and efficacy. (Yes)
7.	Relevant stability studies in accordance with the relevant guidelines have been started with at least one pilot scale or industrial scale batch and at least three months stability data are at the disposal of the applicant. Assurance is given that these studies will be finalised and that the data will be provided immediately to the competent authorities if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed action).

Variation requirements in EU

B.II.b: Manufacturing (mfg process) continued

B.II.b.3 Change in the manufacturing process of the finished product	Conditions to be fulfilled	Documentation to be supplied	Procedure Type
Minor change in the manufacturing process of an immediate release solid oral dosage form or oral solutions	1, 2, 3, 4, 5, 6, 7	1, 3, 4, 6, 7, 8	IA
Substantial changes to a manufacturing process that may have a significant impact on the quality, safety and efficacy of the medicinal product			II

Documentation	
1.	Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format or NTA volume 6B format for veterinary products, as appropriate), including a direct comparison of the present process and the new process
3.	For solid dosage forms: dissolution profile data of one representative production batch and comparative data of the last three batches from the previous process; data on the next two full production batches should be available on request or reported if outside specification (with proposed action). For herbal medicinal products, comparative disintegration data may be acceptable.
4.	Justification for not submitting a new bioequivalence study according to the relevant (Human or Veterinary) guidance on Bioavailability.
6.	Copy of approved release and end-of-shelf life specifications.
7.	Batch analysis data (in a comparative tabulated format) on a minimum of one batch manufactured to both the currently approved and the proposed process. Batch data on the next two full production batches should be made available upon request and reported by the marketing authorisation holder if outside specification (with proposed action).
8.	Declaration that relevant stability studies have been started under ICH conditions (with indication of the batch numbers concerned) and relevant stability parameters have been assessed in at least one pilot scale or industrial scale batch and at least three months satisfactory stability data are at the disposal of the applicant at time of notification and that the stability profile is similar to the currently registered situation. Assurance is given that these studies will be finalised and that the data will be provided immediately to the competent authorities if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed action).

6.Lifecycle Management: Typical Approaches

Higher strength ER tablets

Evaluation of enantiomers and polymorphs

New Indications

Pediatric program

QD product

Novel technology for new routes of administration

Combination product

Registering Higher Strength - MR)

- Fairly common – post approval (ex: 1000 mg vs. 500 mg (approved)
- Read guidance for BA/BE for orally administered drugs
- Needs some development work - Don't assume automatic success
  - Differentiating trade dress
  - Higher strength, larger tablets, may / will dissolve slower
  - Analytical (assay, disso), Formulation, process, scale-up,
- Requires, from pilot scale (> 1/10)
  - Single dose human pivotal BE study
  - If HVD, think about replicated BE study
  - Very technically food effect study and BE at SS
    - Bio waiver can be requested and granted if same technology
    - Via background package
  - ICH Stability (bottles / blisters, bulk, photo)
- Needs Submission and Approval
  - May trigger PAI
  - 6 months review cycle
  - Process validation prior to approval

QD feasibility- Literature Review

TABLE 1

Initial criteria in controlled release feasibility assessments

Physicochemical factors		**Comments**
Dose	<1 mg	Greater development complexity (potential drug content uniformity issue)
	10–250 mg	Average degree of difficulty
	>>250–300 mg	Could need more than one tablet to accommodate the drug load
Dose:solubility ratio (highest dose ÷ lowest solubility in the pH range 1–7.5)	<1 ml	Several technology options exist for CR development
	1–100 ml	Average degree of difficulty
	100–1000 ml	CR development will be challenging but feasible
	>1,000 ml	Need solubilization – CR development will be difficult
	>10,000 ml	CR development practically impossible
Stability	Generally stable as a solid or solution and with common CR excipients	Predict average degree of difficulty
	Compound shows or is predicted to have significant degradation	Predict higher degree of difficulty
Biopharm factors		
Absorption mechanism	Transcellular passive diffusion	Average degree of difficulty
	Other mechanisms including efflux	Performance could be difficult to predict
Regional permeability (colonic absorption)	Poor absorption, $P_{app,\,Caco\text{-}2}<10^{-6}$ cm/s, $k_a<0.01$ min^{-1}	CR formulations with prolonged delivery duration may not be feasible. Likely will not be bioequivalent to IR
	Moderate absorption, $P_{app,\,Caco\text{-}2}=10^{-6}–10^{-5}$ cm/s	CR development challenging but feasible. Might not be bioequivalent to IR
	Good absorption, $P_{app,\,Caco\text{-}2}>10^{-5}$ cm/s, $k_a>0.01$ min^{-1}	CR development should be feasible. Likely to be bioequivalent to IR
PK factors		
PK or PD half life	<1–2 h	Half life too short for CR development
	2–10 h	Acceptable half life
	>>10 h	Compound might not need CR for reducing dosing frequency
Metabolism and efflux	High presystemic or first pass metabolism	Relative BA of CR formulation might be low
	Compound is P-gp or CYP3A4 substrate	CR performance difficult to predict (depends on dose and K_m, V_{max})

Switching from IR → BID or BID → to QD

- Becomes challenging:
  - For drugs having poor solubility at neutral pH (as in weak bases)
  - At high dose (~ > 500 mg)
  - Poor dose / solubility ratio at high pH
  - Inherently low half life (1-2 hrs)
  - Substrates for pGP or CYP3A4
  - Significant FPE

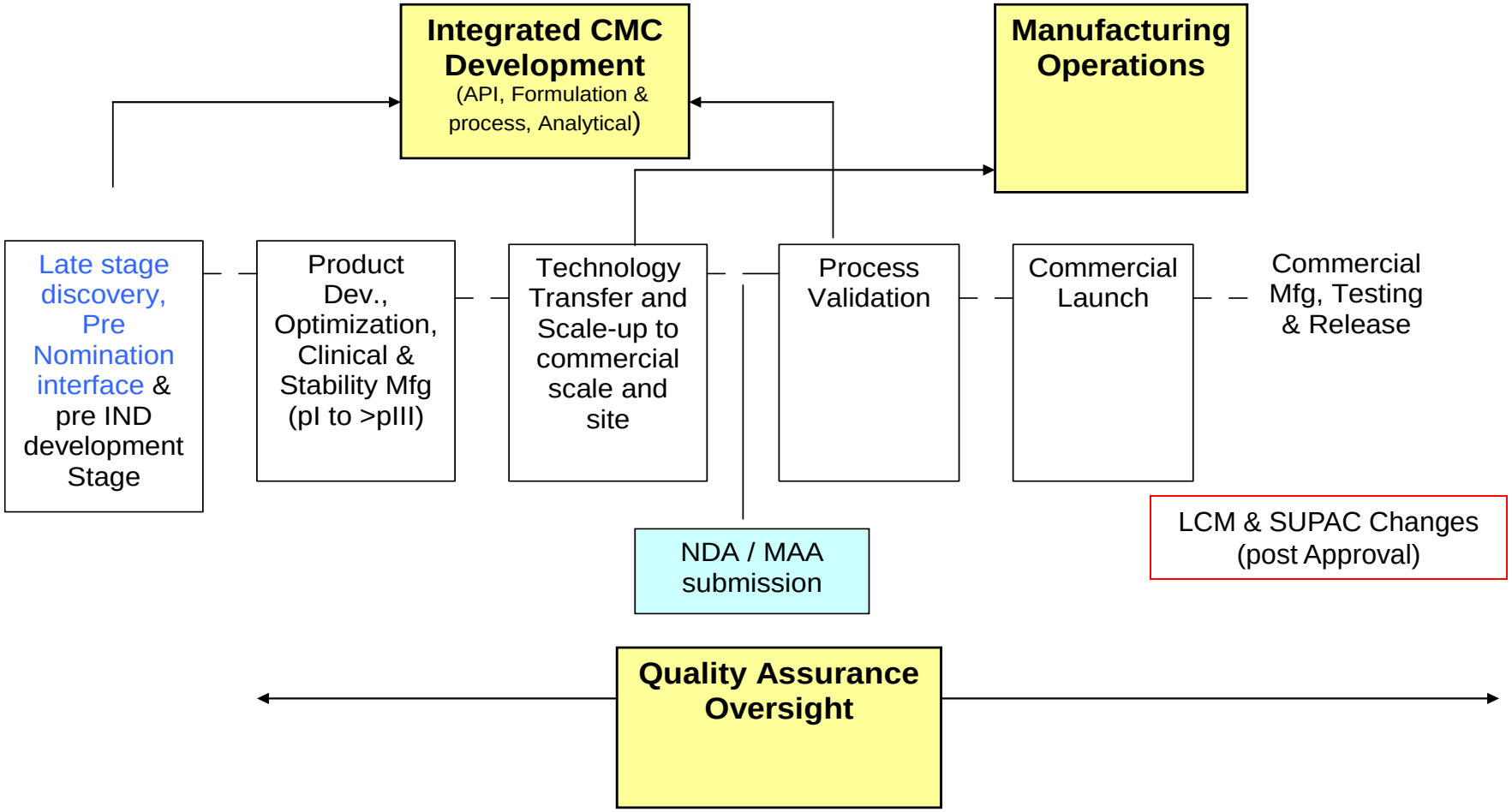
- In vitro: Easy to get 24 release profile (several pH media), 900 ml

- May not translate into in vivo (colon has limited volume: 50 ml)

- Unless suitably manipulated thru Formulation & Drug Delivery Technologies that takes into account physico-chemical properties (physical pharmacy) of drug, GI physiology, Biopharmaceutics aspects

7. Concluding Remarks

Theme - Candidate Nomination to Commercialization



Broad & Clear Allocation of Activities – 1 example Between Product Development & Mfg Ops

CMC / Pharmaceutical Development

- PD Strategy & Timelines
- All pre-IND activities
- IP development
- All pre-NDA submission activities
  - NDA / MAA Drafting
- Development Contracts
- Development Project Driven Demand
  - P1 to P3
- Technical responsibility for process validation (review content of validation protocols and reports)
- Support Initial Launch (bulk) and PACs

Manufacturing Operations

- Define secondary packaging
- Packaging validation
- Commercial Launch
- Routine commercial Mfg, Pkg, and Release
- Commercial Contracts
- Commercial Supply Chain Mgmt
- Manage process validation timelines and logistics
- Post NDA approval activities
- Annual reports

Shared:

- PAI Prep
- Activities during NDA review
- Vendor Selection (pIII & beyond)

Case by Case:

- Second supplier

7. References – QbD, Scale-up, PV, Process Capability

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