Pharmaceutical Development

"Value Add" Component in Drug Development

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CABS, June 5th 2010

Outline

1. Integrated CMC Approaches

2. What is Pharmaceutical Development

3. Critical Steps in Drug Development – Role of PD
   - Discovery → Commercialization & Beyond

4. QbD & Evolution of Quality Engineering

5. Concluding Remarks & References

Dev Costs vs. Regulatory Review vs. Compliance

Dev Costs $: CMC is ~ 33%

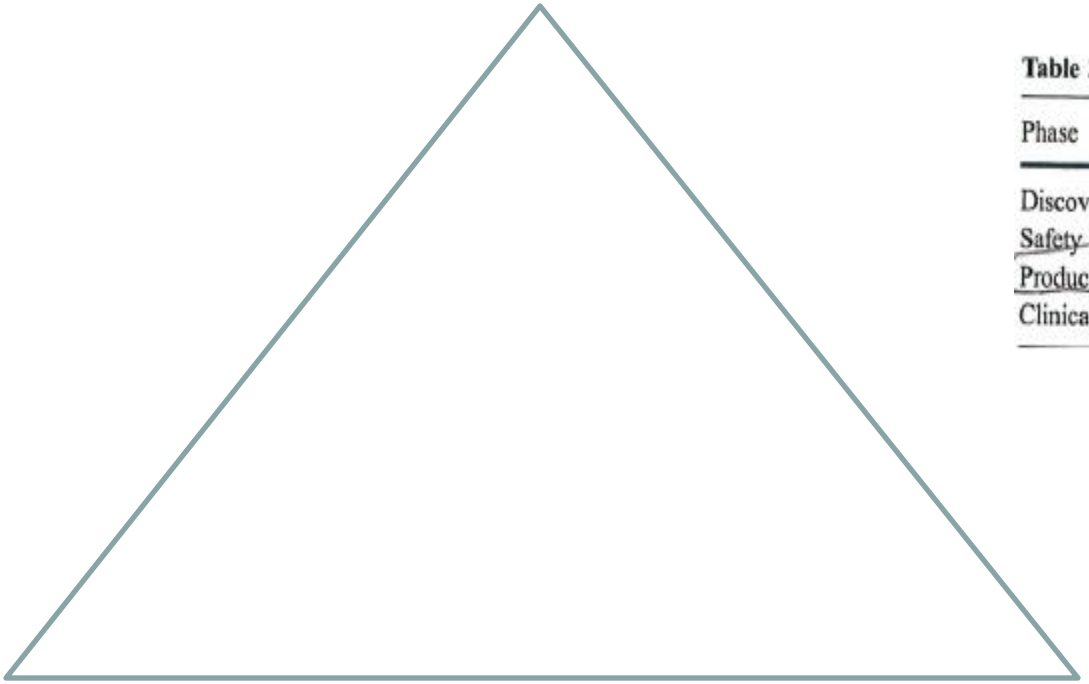


Table 3 Breakup of cost of developing a new drug

Phase	Percentage
Discovery	20–25
Safety and toxicology	15–20
Product Development(Including Clinical supplies)	30–35
Clinical Trials	35–40

J Pharm Innov (2008) 3:175–187

Regulatory Review
pre clinical, CMC, & clinical
CMC: 1/3 or more

GxP: compliance & inspections
GLP, GCP, GMP & PAI
CMC: > 1/3 attention

CMC - Ironies

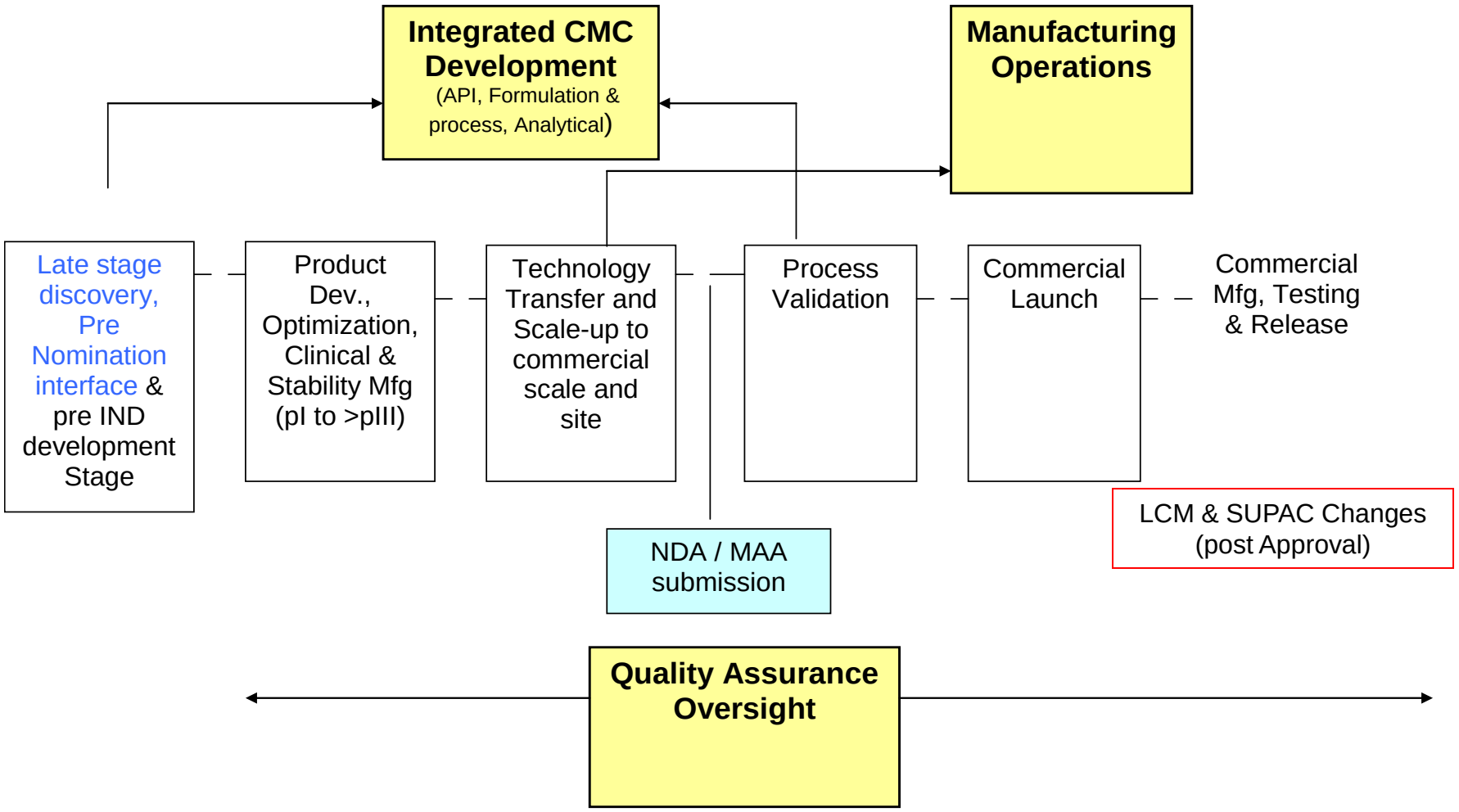
- CMC is combination of many groups:
  - API , Drug Product, Analytical, Packaging….
  - Quality Control / Quality Assurance
  - Regulatory Affairs
- CMC as an academic faculty does not exist
- CMC as single “function” in any organization rarely exists
- “CMC” name, historically stemmed from CMC sections in IND and NDA (Section 4)
- These sections with different flavor are now “Quality” in CTD (3.2 S, 3.2 P, QOS):
  - With portions in Biopharmaceutics & PK (2.7.1)

Pharmaceutical Product - CMC Perspectives

- API or Drug Substance (3.2 S)
- DP - Formulation & Process (3.2P)
  - Portions in Biopharmaceutics summary (2.7.1)
  - Preformualtion goes into 3.2S and 3.2P
- Packaging / container-closure(3.2P):
  - Material Science , Packaging Engineering
- Analytical (3.2P and 3.2 S):
  - Methods, Method validation, Stability
- Polymorph screening, salt screening & salt selection are truly cross functional within CMC (3.2S and 3.2 P)

CMC / Pharmaceutical Development Cycle

Candidate Nomination to Commercialization



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Pharmaceutical Development
Different roles in different industries

- Pharmaceutical Dev= preformulation + formulation + process
- Goal: Develop stable product that meets target product profile
- NCE development: discovery → Commercial Launch & LCM
- ANDA development
- 505 b(2) development
- OTC development
- Excipient development

Not covered in this session

Faculties driving Formulation Development

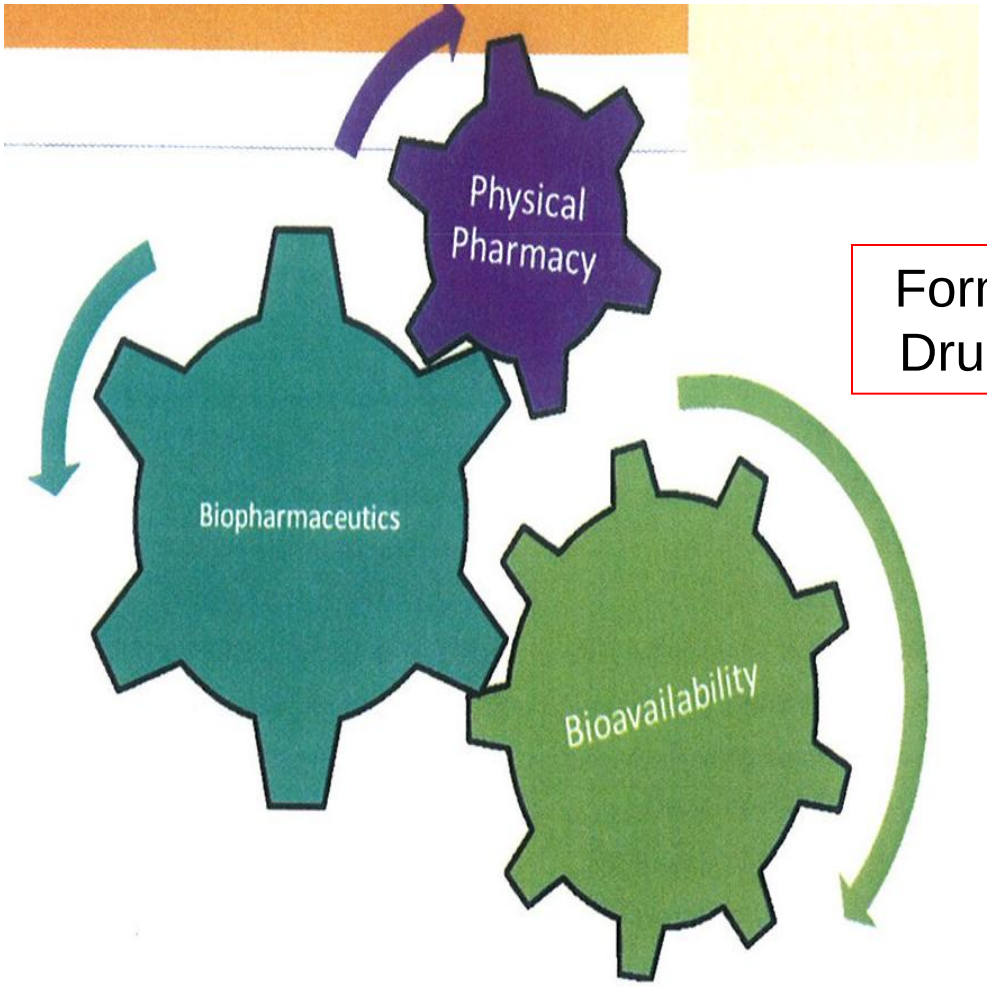
- Pharmaceutics:
  - Science and engineering of converting “API / Lead” into “Drug Product” to meet target product profile
- Biopharmaceutics:
  - Branch of Pharmaceutics that considers the interrelationship of the physicochemical properties of the drug, the dosage form or delivery system in which the drug is given, and the route of administration on the rate and extent of drug absorption
    - PK, is therefore, sub set of Biopharmaceutics
- Physical Pharmacy
  - Physical chemistry related to “drugs” / “API” / “Leads”
- Industrial Pharmacy:
  - Process Engineering aspects to convert API into dosage form / drug delivery system

Formulation Development

- Multidisciplinary, broad based, applied science and engineering

- 2 interplays are of paramount significance
  - Physical Pharmacy – Drug Delivery – Biopharmaceutics
  - Material science – Formulation – Process engineering

Physical Pharmacy – Formulation / drug delivery - Biopharmaceutics



Physical Pharmacy

(pKa, solubility (Aq, pH), IDR, logP / LogD, Form, etc)

Formulation & Drug Delivery

Biopharmaceutics

Desired PK /PD
Safety / Efficacy

Biopharmaceutics is link between (CMC + Drug delivery) & (Clinical Efficacy & PD)

Material Science – Formulation – Process Engineering

Chemical Properties

- Molecular structure
- Molecular Wt
- Partition Coefficient
- Ionization (pKa)
- Solubility Product (Ksp)
- Stability :
  - Solution
  - Solid state
  - Photolytic
  - Oxidation

Physical Properties

- Polymorphic Form (s)
- Crystallinity
- Melting point
- Particle size, shape, surface area, density, porosity (micromeritcis)
- Hygroscopicity
- Solubility
- Dissolution Rate
- Wettability

Mechanical Properties

- Elasticity (stiffness)
- Plasticity (hardness)
- Viscoelasticity
- Brittleness
- Tensile strength
- Bonding

Preformulation

Manufacturing

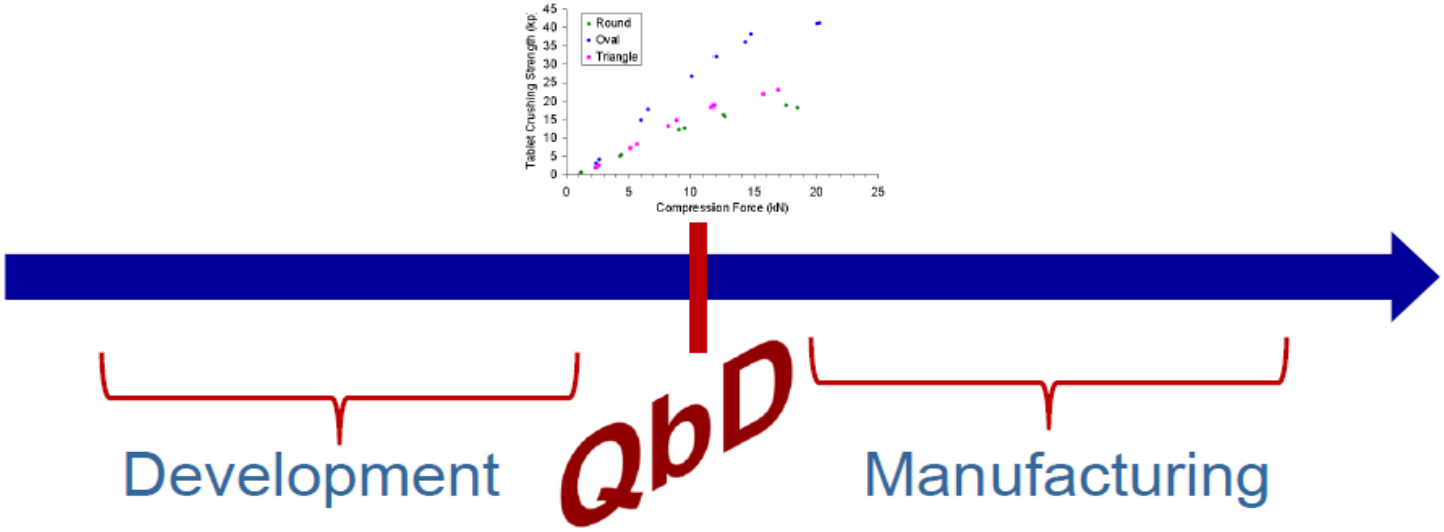
Discovery / Lead Selection

Formulation / Process Engineering

Geg Amidon, AAPS Webinar on mechanical properties

Role of Pharmaceutical Scientist

- To identify a formulation and processing that yields a manufacturable formulation with the desired critical product attributes (ie: Development phase)
- Does it every time (ie: Manufacturing phase)



Prof Greg Amidon, AAPS Webinar, 6/2009

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Critical Stages – Where PD adds Value

Discovery

Product Development
Support clinical & commercial

Commercial

Pre Candidate Nomination

Pre IND and pI start (FIH)

pII → pIII & ICH Stability, Scale-up

PAI prep, Process Validation, Launch Mfg

LCM & SUPAC changes

Quality Risk Assessment
QRA 1: After phase I
QRA 2: Prior to phase III

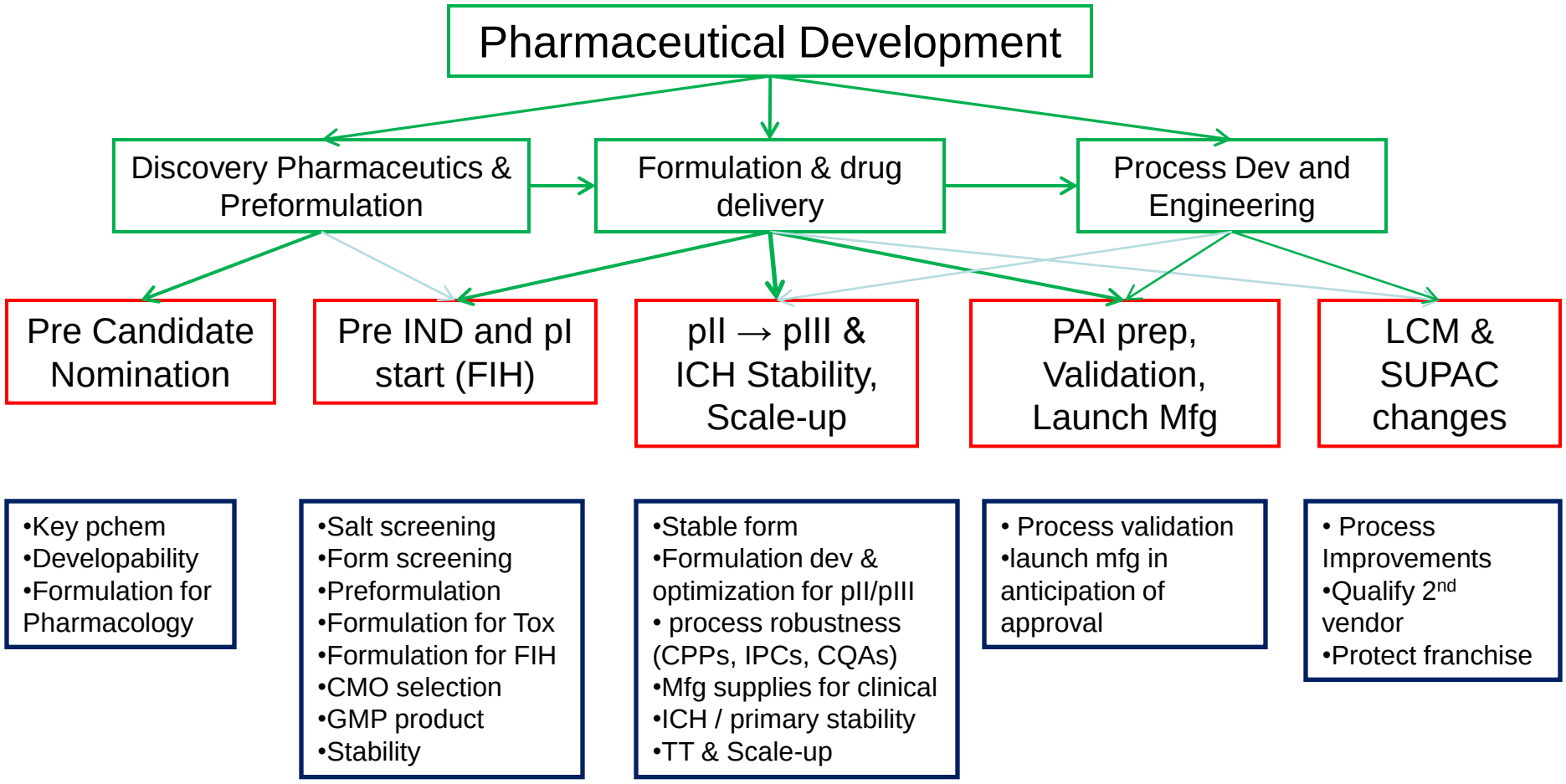
Candidate selected for Development

IND submitted

NDA submission

NDA Approved

Critical Stages – How PD adds Value



Discovery: Pre candidate Nomination

Input Needs

1. Chemical structure / mol wt
2. clogP, predicted pKa
3. Lead material needs (<< 1 gm) for property
4. Material needs for formulation support for Pharmacology / ADME (x gm)

Strategize

1. What are the main properties need to be assessed

Out put Deliverables

1. Formulation support for Pharmacology / ADME
2. Critical pharmaceutical property Assessment
3. Developability risk assessment
4. PD plans for next stage (post nomination to IND):
   - A. Timing and need for polymorphs and salt screening
   - B. GLP Tox formulation
   - C. FIH formulation

Iterative loop on Formulations for Pharmacology

Pharmaceutical evaluation of early development candidates "the 100 mg-approach"

International Journal of Pharmaceutics 275 (2004) 1–12

Stefan Balbach*, Christian Korn

Abstract

Early development candidates are often selected for pre-clinical and clinical development based primarily on pharmacological and toxicological data. In order to choose the best compounds from a biopharmaceutical point of view, physicochemical parameters such as solubility, dissolution rate, hygroscopicity, lipophilicity, pK_a, stability, polymorphism and particle characteristics need to be evaluated as early as possible and above all with the highest accuracy. However, the low amounts of drug substance available in early development often compromise data quality, and therefore, hamper an early pharmaceutical assessment. This article summarises the Aventis approach on early pharmaceutical compound profiling with the aim of providing a high quality assessment requiring not more than 100 mg of drug substance. In particular, the evaluation criteria, process and miniaturised analytical technology that can be applied for this purpose are discussed.

In reality: 500-800 mg

Property Assessment & Relevant Risks

Biopharmaceutics Risks (PK, Exposure, absorption)

- Ionization (pKa)
- Solubility (Eq, Kinetic)
- IDR
- Log P/Log D
- Solubility limited vs. dissolution rate limited

Stability, Polymorphism, Manufacturing Risks

- Crystallinity, Melting Point
- Propensity for polymorphism & solid state stability
- Chemical stability
- Hygroscopicity

Developability Assessment - Broad Vision

- Not a black and white criteria to reject or nominate a candidate

- Rather, strategic tool for "risk assessment
  - Absorption & exposure risks:
    - Solubility vs. dissolution rate vs. permeability
  - Stability risks
  - Solid state and polymorphism risks
  - Handling & processing risks (Hygroscopicity, melting point, etc)

- Not all risks & impacts are same

Nomination to → IND submission & Start pI

Input Needs

1. Critical pharmaceutical property & Developability Assessment
2. API needs:
   1. For GLP formulations
   2. Formulation dev for FIH
   3. GMP supplies for FIH

Strategize Plans

1. Refine Target Product Profile for phase I
2. Vendor selection
3. Dosage form for pre clinical vs. FIH
4. Enabling technologies ?

Out put Deliverables

Preformulation
Drug-excipient compatibility
pH stability, pH solubility
Salt selected (or not)
Form screening

Prelicnial
Formulation for Tox
Enabling Tehcnolgies

Phase I clinical
Formulation & Process
GMP supplies
Adequate Stability

IND
Drafting DP sections (3.2P)

QRA1 & Plans for pII

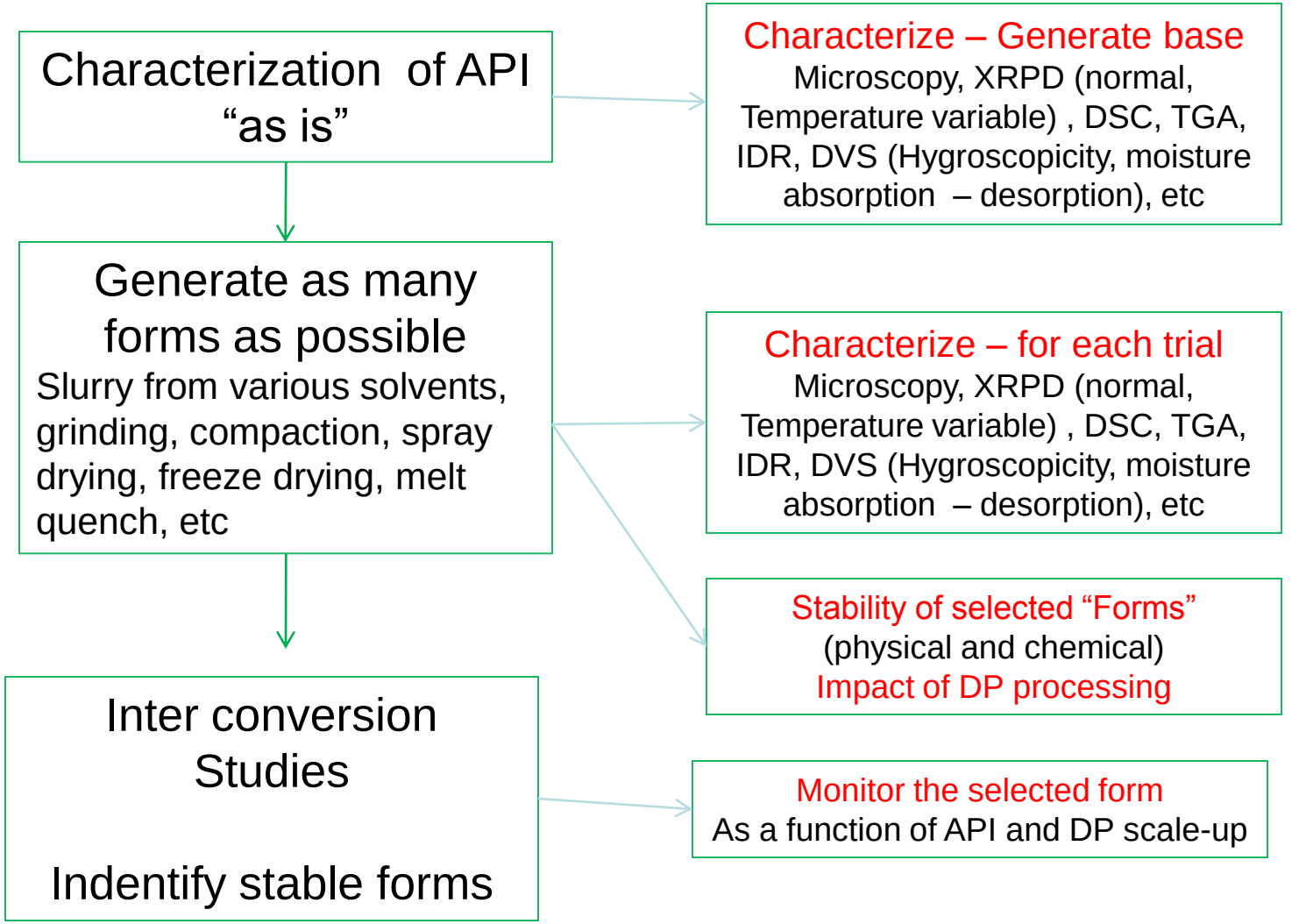
Tox formulations are more challenging
Challenges: ↑ dose; API not well characterized
Pus: don't worry about long (er) term stability

Polymorphic forms

- Two polymorphic forms can be as different as two different compounds
  - Crystal habit
  - Melting point and sublimation temperature
  - Solubility and dissolution rate
  - Density, crystal hardness, compactability
  - Optical Properties, Stability & Reactivity

- Two ends of the spectrum:
  - Amorphous : high energy; ↑ solubility / DR; Less stable; more hygroscopic; more reactive (not preferred for development, but OK for pre clinical)
  - Crystalline: ↓ solubility / DR; but more stable (preferred for dev & registration)

Broad Approach for Form Screening (How)



Strategizing dosage form selection
(in the context of current generation of NCEs – Oral Route)

Dosage Form	Pre Clinical Tox	FIH & pI	pII	pIII & beyond
Solution	Yes; but not possible[1]	Yes; but not possible	No	No
Suspension	Yes; but may not work[1]	Yes; will need taste masking	No	No
Enabling formulation Technologies	May be needed	Not preferred; but may be warranted		
Powder In Capsule / Powder in bottle	No	Yes; preferred by some	No	No
Capsule	Yes (in dog)	Yes	Yes	Yes
Tablet	No	No	Yes	Yes

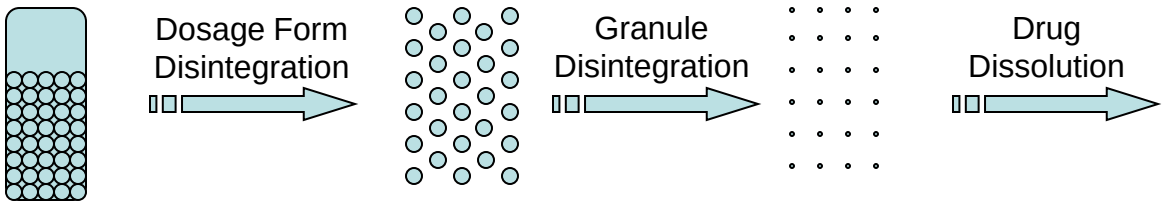
[1] for current generation of poorly soluble drugs

My bias: start with Capsules (μ API + formulation) in FIH .....plan to switch to tablets in phase II & beyond

A possible formulation even for poorly soluble (HG capsule in phase I → Tablet in phase II)

Component	Function
API	micronized API
Lactose / Mannitol	diluent (helps to disperse µ API)
Sodium Laurul Sulfate	wetting agent (helps re dispersion in GI milieu)
Povidone K-29/32	binder
Croscarmellose sodium	disintegrant
Colloidal silicon dioxide	glidant
Magnesium stearate	lubricant
Purified water	granulating fluid

Stages in drug dissolution:



Support Clinical Development – pII

Input Needs

1. Salt finalized
2. QRA 1 completed
5. API needs
   1. Product Dev
   2. GMP supplies – remaining pI, pII, pIII
   3. Chronic Tox

Strategize Plans

1. Refine Target Product Profile
2. When and how to introduce TBM (to be marketed product)
3. QbD and product optimization
4. Mfg at smaller scale

Out put Deliverables

Pharm. Development
- Select stable "form"
- Product developed and "Optimized"
- Adequate stability
- Interim PD report (s)

Clinical
- GMP supplies for pII

Regulatory
- EOP2 CMC
- IND amendments

IP ?

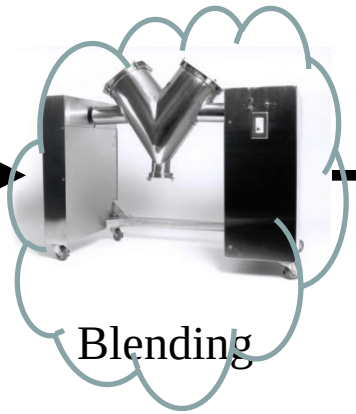
Think about phase III and Commercial as you are developing product for pII

Advantages of Solid Dosage Forms

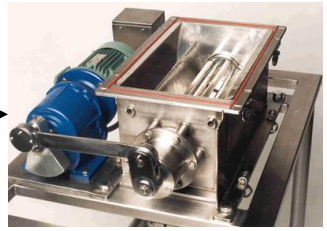
- Most convenient dosage form for the patients
- Tailor made release profile can be achieved
- Accuracy of dose is maintained
- Improved Organoleptic properties (taste, appearance and odor)
- Non sterile dosage form, stringent environmental conditions not required
- Longer expiry period; RT Storage
- Renders for trade dress (color, id, differentiation, branding)
- ↓ COGs, ↑ throughput, scalable, transferable across CMOs

Tablet & Capsule Manufacturing Processes

Weighing / Dispensing



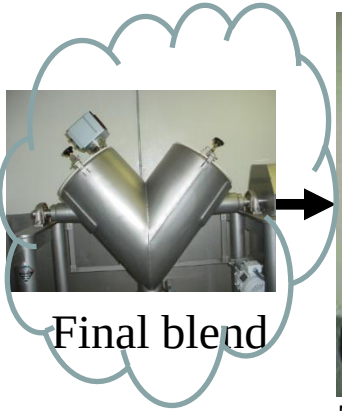
Blending



Granulation

Drying

Milling



Final blend

Tabletting / Encapsulation

In-process check

Coating

QC Check

Develop robust process; understand input – output relationships

Excipients – Don’t Ignore !

- Enablers of medicinal products
  - Conversion of APIs into safe and efficacious medicinal products
- “inert” / Inactive Ingredients
- Acceptable physical & chemical compatibility with API
- Excipient generally not pharmacologically active, but may directly or indirectly exert…..
  - Physical effects (i.e. modified release)
  - Chemical effects (i.e. micro environmental pH)
  - Physico-chemical effects (i.e. solubilization, dissolution rate)
  - Absorption enhancers (pGp inhibition by Vit E TPGS)
- Global Registration;
  - Compendia, within IIG levels, TSE/BSE free, global availability
- Functionality Testing……Knowledge of material science & Formulation

Phase III batches (pivotal efficacy)

Pivotal efficacy is a key basis for approval
Data from DP lots in phase III help refine specifications
Bridging pIII to future anticipated changes

Input Needs

Lock formulation and process; process optimized ; stability established

EOP 2 CMC meeting with FDA

Test Method Validation completed

Documentation
MBRs, **Mfg protocol**, TMs, specifications

Stability Protocols
(CTM / ICH)

Strategize Plans

1. X DP batches / strength (based on clincial design)
2. At pilot scale > 1/10 or 100,000 units whichever is larger

Output Deliverables

X batches mfg & released Bulk and CTM Packaged

Executed batch record in NDA

Establish basis for commercial scale-up and Process validation

Can be combined with ICH / stability batches

ICH Stability batches (aka primary stability)

A key milestone in overall drug development
Requirement: file with 12 months data
- ICH Q1A (DS and DP); ICH Q1B (photo stability)
- ICH Q1E (evaluation of stability data)

Input Needs

Pilot scale formulation & and process optimized ; core process locked

Documentation
MBRs, Mfg protocol, TMs, specifications

Container-closure for Mktg defined

ICH Stability Protocols
Packaged Product, Bulk, Product, Photo stability

3 lots of DS
(representative of commercial supply chain

Strategize Plans

1. 3 DP batches / strength with Trade Dress
2. At pilot scale > 1/10 or 100,000 units whichever is larger

Output Deliverables

3 batches mfg & released
Bulk and Packaged

Stability Clock initiated
(pkg, bulk, photo)

Executed batch record in NDA

Establish basis for commercial scale-up and Process validation

Expected Shelf Life in general
For RT storage: y=1.5X; but NMT X+6 (check ICH Q1E)

Technology Transfer & Scale-up

- 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

Product Development Reports
(Pharmaceutical Dev. Reports)

- No Statutory Requirement……..but
- Meet requirements of “Pharmaceutical Development” in CTD (3.2.P.2) and ICH Q8 guidance
- Discrete pharmaceutical dev. reports to support submission:
  - Development: Preformulation, formulation development, compatibility, container – closure. Manufacturing process development (CPPs, IPC, CQAs),
  - Scale-up
- Product Development report expected during PAI:
  - Integrated Report ……Development “song”
  - Rationalize TBM product (formulation & process)
  - Link pivotal efficacy & ICH batches to proposed commercial
- Simple, succinct……
- Good business practice; serves Business Development DD

PAI Preparation

- Expected within 4-10 months of filing:
- Process…….not an event
- Preparation Starts before phase III batches
- Team work (QA Lead, CMC co Lead, SMEs)
- Develop Checklist and Manage – custom to a program
- Ensure all development issues are identified and covered
  - Product Development Report
  - Process Validation Protocol
- Master the art of Managing CMOs remotely
- PAI mock inspections

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

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

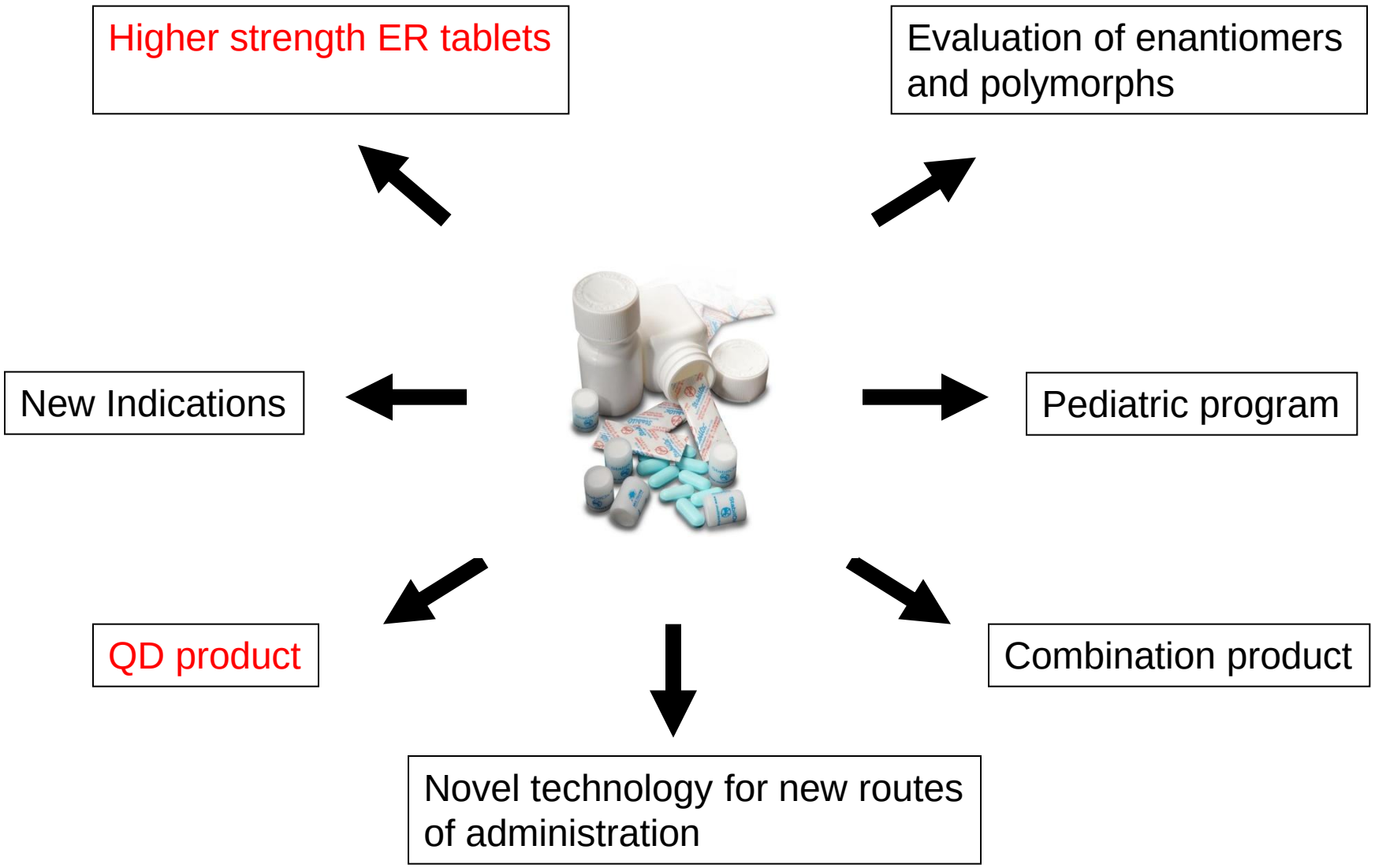
Batches can be sold

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

IP – leading to Orange book listed patents

- By design, accident, serendipity
- Novel, not obvious, utility, not frivolous
- Orange book Listed patents
  - http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm
  - Drug substance (composition of matter)
  - Drug product & method of use
- File timely invention disclosures
- Formulation and drug delivery has given new life even in NCE development…….prior to approval

Lifecycle Management: Typical Approaches



Scale-up and Post Approval Changes (SUPAC)

- Guidance:
  - Post Approval Change (PAC) guidance
  - SUCPAC-IR, SUAPC-MR
  - Equipment Addendum for SUAPC IR and SUAPC MR
  - Biopharmaceutics (BA/BE, Biowaiver, etc)

- 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

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

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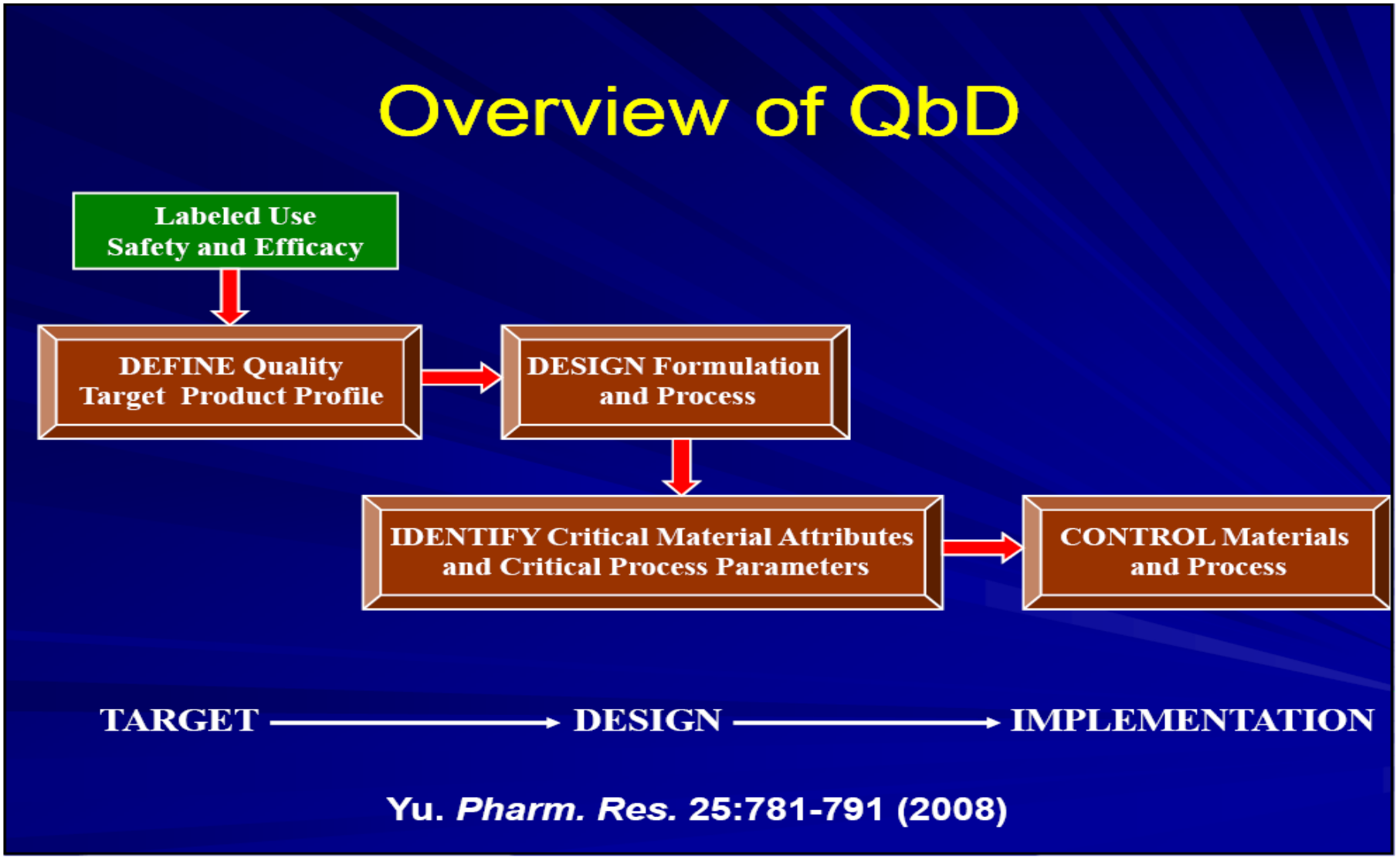
QbD Backdrop

- ICH Q8 (R2) Guidance – Pharmaceutical Development
- Current CMC regulatory paradigms at FDA and EMEA
- Key premise:
  - Quality cannot be tested into products; quality can only be built into products
  - Pharmaceutical QbD is a systematic approach that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management

General Schematics



Key Elements of QbD

- Define Quality Target Product Profile (QTPP)
- Design and develop product and manufacturing processes; establish design space
- Identify:
  - Critical Process Parameters (CPPs); Critical Quality Attributes (CQA –Ys)
  - Sources of variability
- Compute Statistical Process Capability (Cpk)

$$\text{Process capability index } (C_pK) = \frac{\text{Upper limit of specification} - \text{lower limit of specification}}{6 \text{ standard deviation}}$$

- Control strategy to produce consistent quality over time

Quality Target Product Profile (QTPP)
Consistent per ICH Q8 (Pharm Dev)

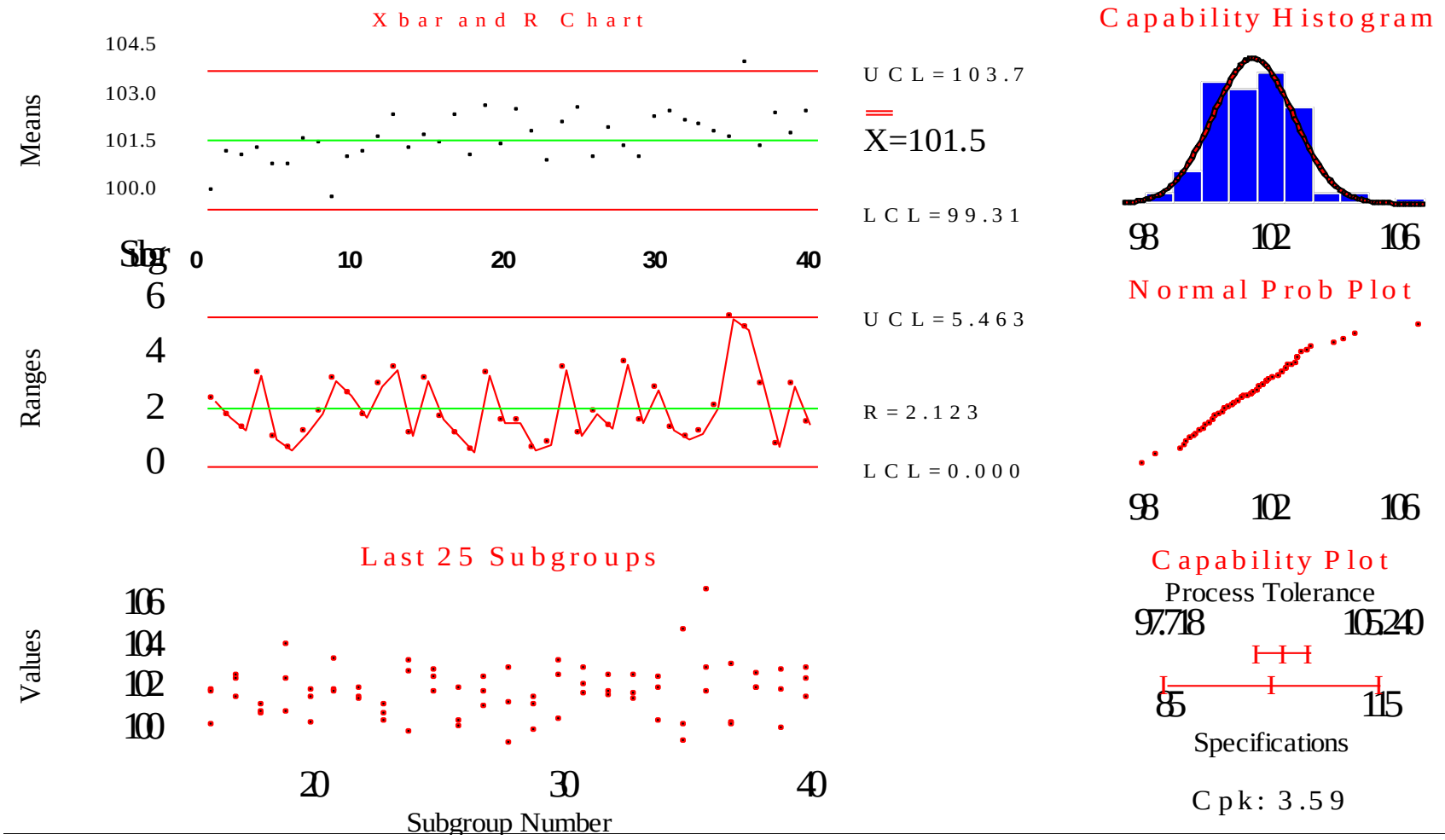
- Key Objective: Help guide pharmaceutical development, expected per QbD paradigm
- Premise: Evolutionary in nature…….as function of clinical development

Parameter	Desired Target pI	Desired Target for TBM
API	X	X
Strength (mg)	10, 100	60
Route of Administration	Oral	Oral
Dosage Form	Powder in capsule	Tablet
Frequency	N/A	BID
Release Characteristics	Immediate release	Modified release
Quality Attributes	Id, Assay, Impurity, Fill wts, UOD	Id, Assay/Impurities, Disso, Moisture, UOD
Stability	Minimum: 1Q beyond duration of clinical study	24 M at controlled RT
Container-closure	20 ct in any size HDPE bottles	14 ct, 60 ct, 500 ct in HDPE bottles with CRC
Supply chain	Single source	API is dual sourced; but 2nd supplier for DP after approval

MINITAB Six Pack- Commercial Scale

Benchmark: $C_{pk} > 2$

Commercial Scale - CU for Compression Run



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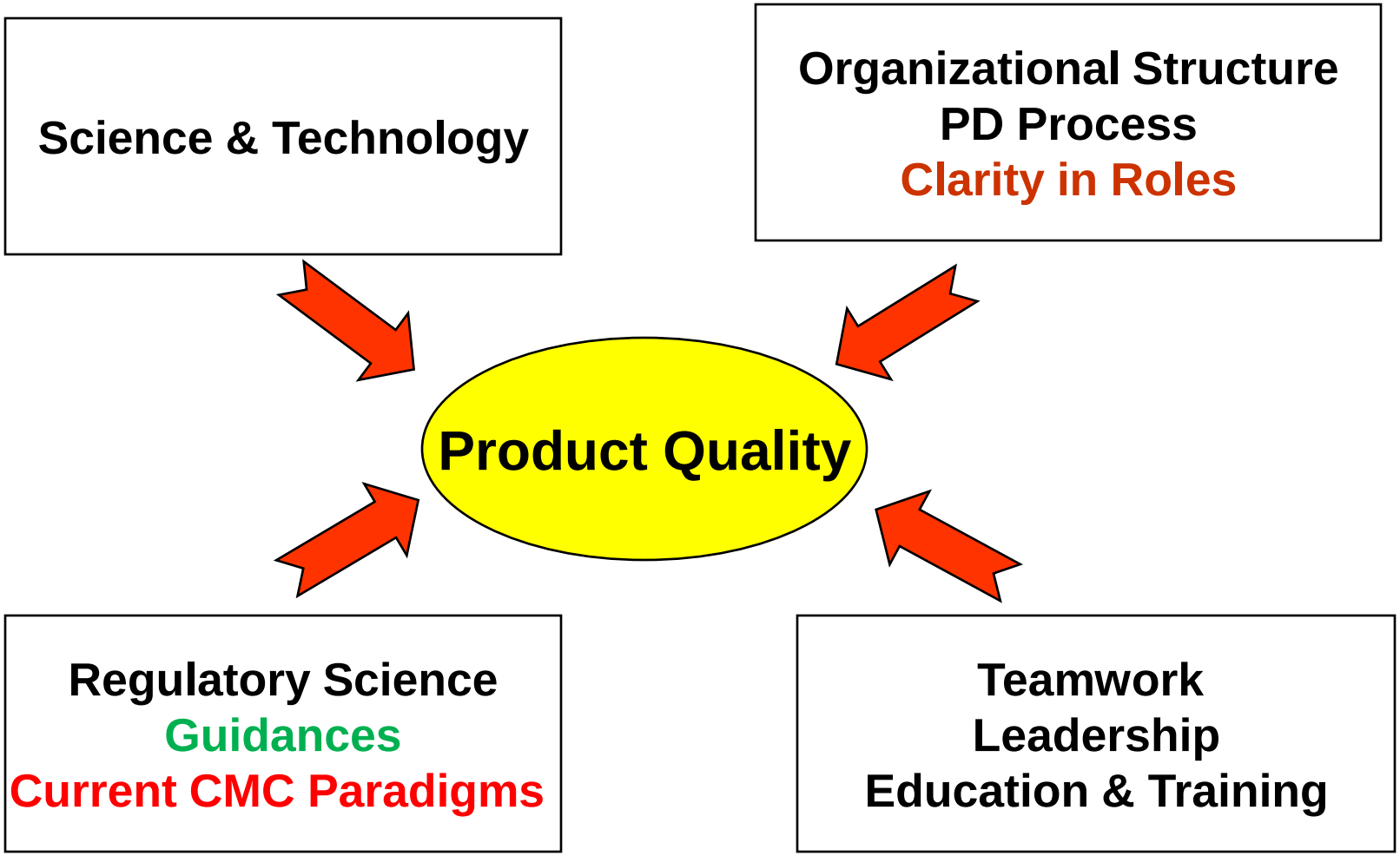
PD - Adds value along multiple dimensions

- Lead pharmaceutical Developability risk assessment during candidate selection (from discovery)
- Develop and supply formulations (& processes), for Tox and clinical trials (pre IND and Clinical Development)
- Develop robust formulation & process (Registration)
- Lead Technology Transfer & Scale-up (Approval enabling)
- Lead Process Validation and Launch Mfg (commercial enabling)
- Create patents leading to “orange book listing” (IP)
- Support / Lead LCM initiatives (post approval)
- Manage SUPAC / PAC (post approval)
- CMC lead to facilitate due diligence for In/out Licensing (BD)

Drivers to Product Quality



Thank You ☺; Any ?

References

Relevant FDA & ICH Guidance

- ICH Guidance:
  - ICH Q1A: Stability testing of new drug substances and new drug products
  - ICH Q1B: Stability testing of new drug substances and new drug products
  - ICH Q1D: Bracketing and matrixing designs for stability testing of new drug substances and new drug products
  - ICH Q1E: Evaluation of stability data
  - ICH Q6: Test Procedure and Acceptance criteria for new DS and DP with decision trees
  - ICH Q8 (R2) (2009): Pharmaceutical Development
  - ICH Q9: Quality Risk Assessment
  - ICH Q10: Quality Systems
- FDA Guidances on SUPAC
  - Changes to approved NDA / ANDA
  - SUPAC IR, SUPAC MR, SUPAC SS (non sterile)
  - SUPA IR/Mrand SUPAC SS Manufacturing Equipment Addendum
- Biopharmaceutics:
  - BA / BE studies for orally administered drug products – general considerations
  - Dissolution testing of IR solid oral dosage forms
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