Quality System

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Regulator's Responsibility

"It is not only for what we do that we are held responsible, but also for what we do not do."

Moliere, 17th Century

Quality ?

- **“Freedom from Defects”**
- **“Meeting or exceeding expectations”**
- **“Delivers the properties described on the label”**
- **“Fitness for intended use”**

Can the Patient see quality?

Patient Expects Quality

Can the Patients ensure quality?

They delegate this responsibility to Regulators because

Regulators are

- **Qualified**
- **Trained and**
- **Authorized**

Prescribers and Patients ~~expects~~ assumes

Drugs:

- Safe and Effective
- Delivers the same performance as stated on the label
- Made in a manner that ensures quality
- Available when needed

All built into a "quality" product

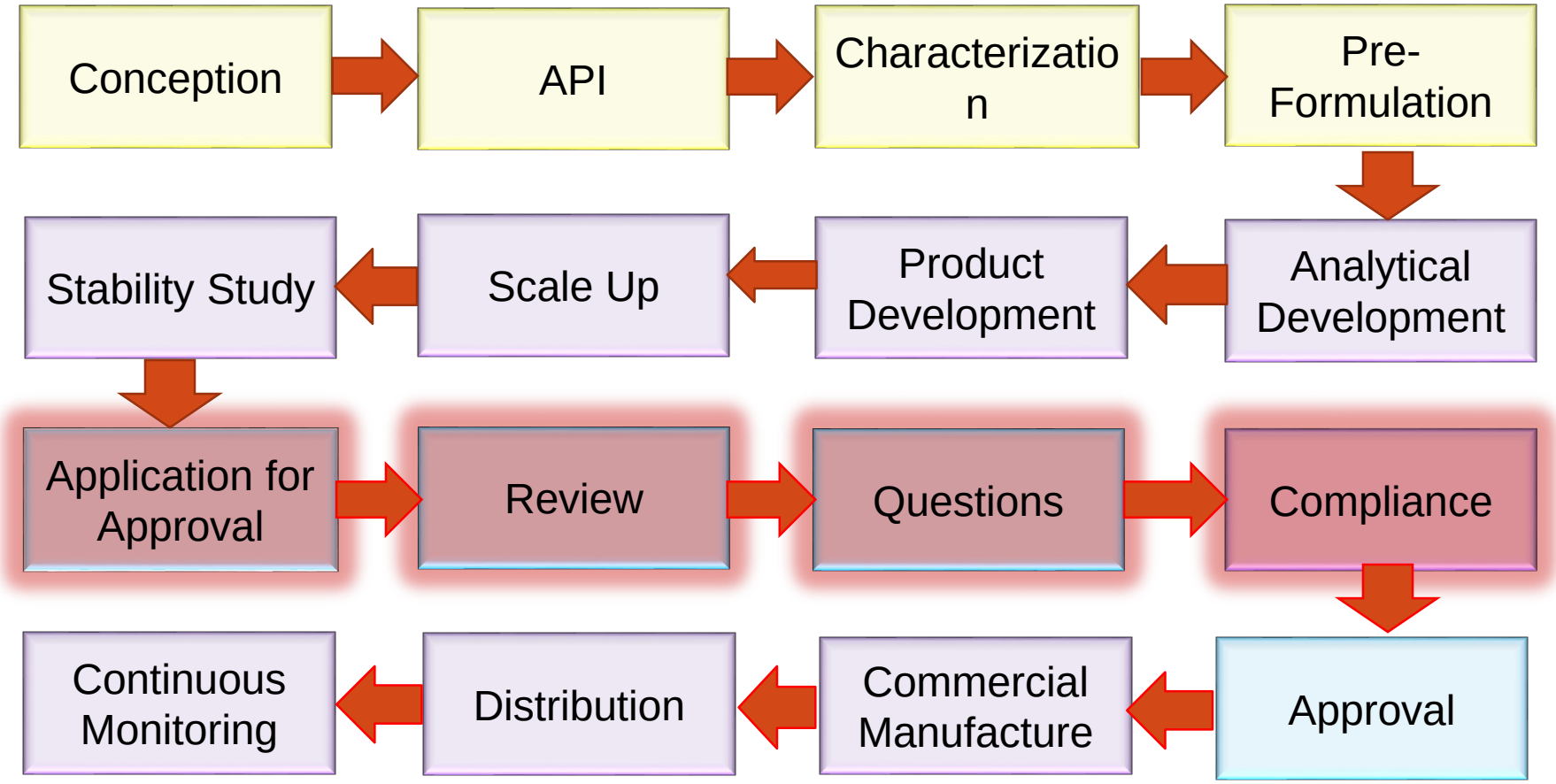
Quality by

- **Design**
- **Accident**
- **Testing**

How do we build in quality?

QbD---→ Understand the Product Life Cycle

Typical Product Lifecycle



Science behind Product Development

- Chemistry: organic, inorganic and physical
- Pharmaceutics
- Chemical Engineering
- Toxicology, Pharmacology, and Pharmacotherapeutics

Product Development

- API
- Excipients
- Process Aids
- Manufacturing Process
- Package System (Drug Delivery)

.....Product Development

- Analytical Methods
- Stability of Product
- Cleaning between the batches and between the products

API

- Source & Availability
- Impurities/Related Substances
- Residual Solvents
- KSM
- GMP

API-Characterization

- **Particle Size**
- **Solubility: Hydrophilic vs Lipophilic**
- **Solubility and pH**
- **Polymorphism & Chirality**
- **Stability**

API-Characterization-Polymorphism

RITONAVIR –protease inhibitor:

Originally thought to have a single crystal form

-Poorly absorbed molecule

-Formulated as soft gel capsule containing an ethanol/water solution of the molecule

Two years after market introduction several batches failed dissolution specifications

A new crystal form precipitated out of solution, this form had ~ 50% lower intrinsic solubility

Product had to be withdrawn from market and reformulated in an oily vehicle

API-Characterization-Polymorphism

Atorvastatin Calcium

– about 27 polymorphic forms reported in literature

-The marketed product - amorphous

API-Characterization-Solubility

Poorly soluble APIs:

- Poor dissolution rate
- Low and variable bioavailability
- More potential for food effect
- Formulation difficulties

Analytical Methods

- Specific
- Precise
- Accurate
- Robust

Analytical Instruments

- **Qualified**
- **Calibrated**
- **Metadata**
- **Audit Trails**

Challenging Dosage Forms

- Suspensions and Emulsions
- Sterile Products
- ER, MR and SR Products
- MDI. DPIs, Nasal Delivery, Topical Delivery
- Proteins, Peptides and Biologicals

Products (QbD)

- QTPP
- CQA's
- CMA's
- CPP's
- CS's

Product Stability

- Storage Condition
- Expiration Dating
- Sterility
- Dose Delivery
- Interaction of Container Closure
- Photostability and Thermal cycling
- In-use stability

Bioequivalence

- **Pharmacodynamic vs Pharmacokinetics**
- **Analytes: Active vs metabolite**
- **Study Design: Cross over vs parallel**
- **Bioanalytical methods**
- **90% CI**

Challenges – Pharmaceutical Equivalency

- Stability
- Impurities ? Mutagenic and Carcinogenic
- Residual Solvents ?
- Dissolution
- pKa
- Scoring
- CU

Challenges – Bioequivalence

- Physiological factors
- Pharmaceutical factors (design)
- Special category of products:

  MDIs, DPIs, Topical Products, Nasal Products

…….Challenges – Bioequivalence

- Highly variable drug products CV_{intra} >30%

  Ex: Progesterone capsules, Fenofibrate
- NTI: Levothyroxine, Carbamazepine, Phenytoin, Digoxin, Cyclosporine, Sirolimus, Theophylline etc.
- **IVIVC**

What does a Regulator expect?

Therapeutic Equivalence

Therapeutic Equivalence

Pharmaceutical Equivalent:

Drug products are considered pharmaceutical equivalents if they contain the same active ingredient(s), same dosage form, route of administration and are identical in strength or concentration

…..Pharmaceutical Equivalent

Exception:

……..but they may differ in characteristics such as shape, scoring configuration, release mechanisms, packaging, excipients (including colors, flavors, preservatives), expiration time, and, within certain limits, labeling.

Do not get confused with Pharmaceutical Alternative

Same therapeutic moiety, but different salts, esters, or complexes of that moiety, or are different dosage forms or strengths

(e.g., tetracycline hydrochloride, 250mg capsules vs. tetracycline phosphate complex, 250mg capsules; quinidine sulfate, 200mg tablets vs. quinidine sulfate, 200mg capsules)

Therapeutic Equivalent

Pharmaceutical equivalent +

……..Therapeutic Equivalent

Pharmaceutical equivalent +

same clinical effect and safety profile when administered to patients under the conditions specified in the labeling.

……..Therapeutic Equivalent- General Criteria

1. Safe and effective
2. Pharmaceutical equivalent (same……)

   Meet compendial or other applicable standards of strength, quality, purity and identity
3. Bioequivalent-

   meet an *in-vitro* standard

……..Therapeutic Equivalent- General Criteria

4. Adequately Labeled
5. Manufactured under cGMP

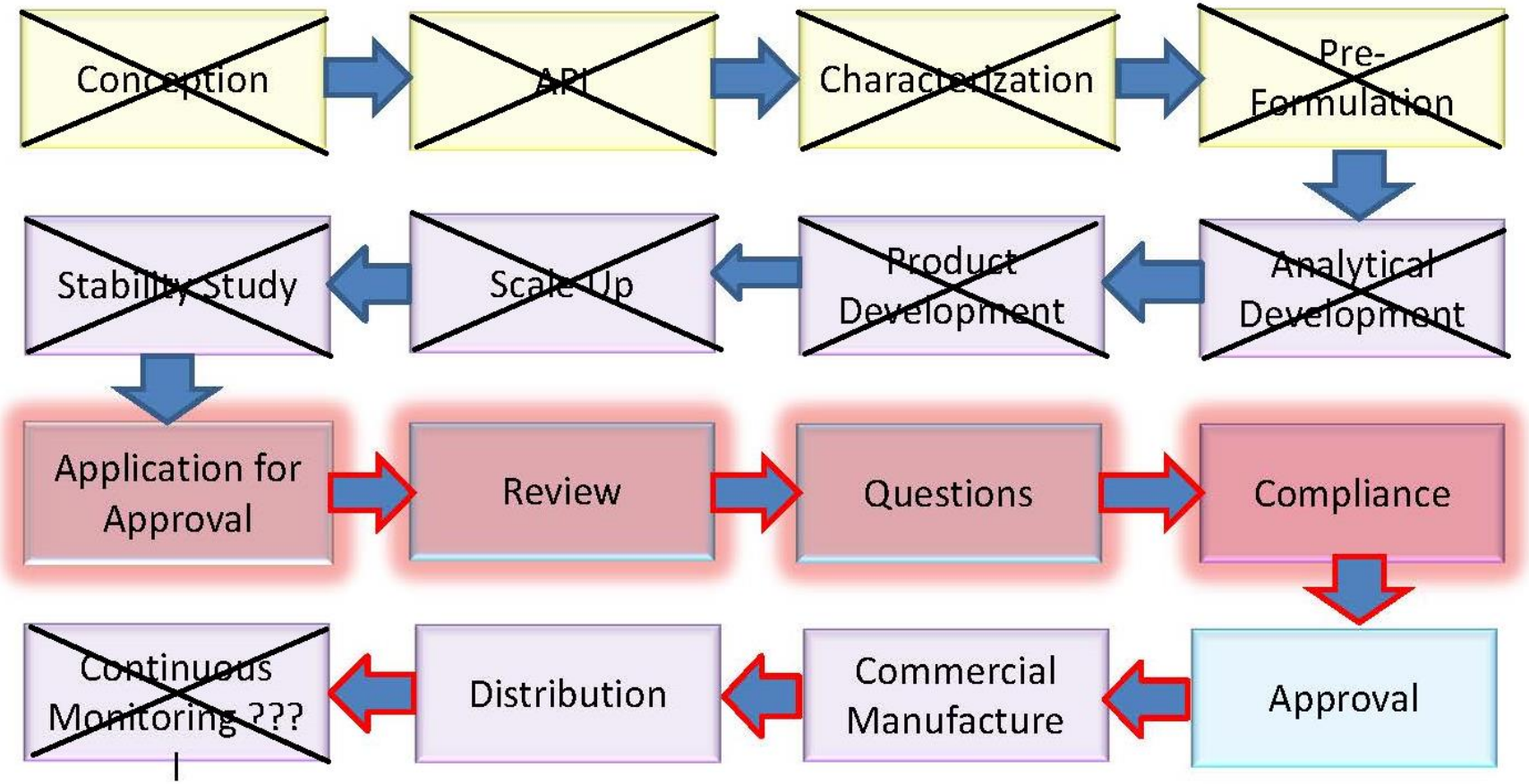
Pharmaceutical Equivalent

- **Equivalent to what?**
- **Why do we need a comparator?**
- **Generics of what?**
- **Is it right to insist Prescribers to write generic names of medicines?**
- **Are all generic medicines pharmaceutically equivalent ---------→ Therapeutically equivalent?**

Recap

- **Typical Product Life Cycle**
- **What is the current scenario?**

Product Life Cycle Management -- Current Scenario



Challenges for Skipping some steps in Product Life Cycle

- Product variability
- Product Stability
- Press & Publicity
- Market Complaints
  - Ineffective
  - Contamination
  - Changes in Appearance

Burden on Regulators for Skipping some steps in Product Life Cycle

- **Responsibility on <u>Regulator rather than Manufacturer</u>**
  - **Forms 17, 17A, 18, 13**
  - **Form 15s**
  - **Form 16s**
  - **Investigation**
  - **Court Cases**
  - **Recalls?**
  - **Answering press, public, legislators, government etc.**

Societal Impact for Skipping some steps in Product Life Cycle

- **Credibility of the regulated product**
- **Public Confidence on the DCA**
- **Self Esteem of the officers**
- **Disturbance in the Supply Chain**

What is the need of the hour?

- Attitude Change
- Introspection in product approval process
- Applying science
- Continuous learning
- Adopting proven regulatory approaches

Goal

To Assure the Prescribers and Public:

Pharmaceutical equivalent drugs are therapeutic equivalent

Questions??????

Thank you