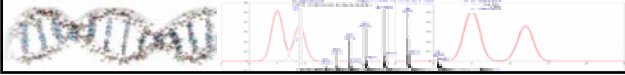


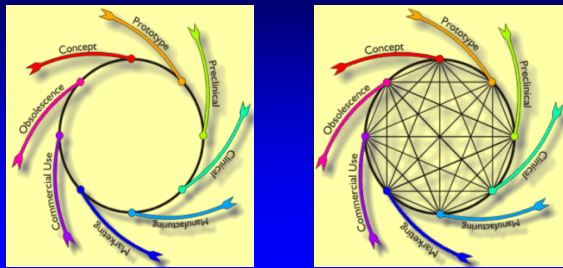
Analytical Lifecycle Management Perspectives for Product Development

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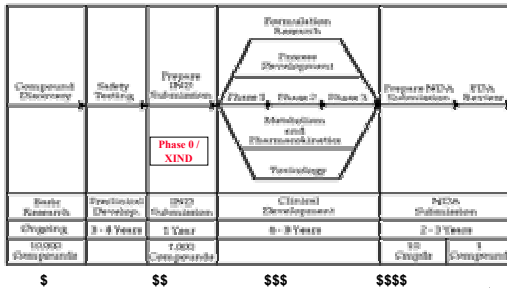


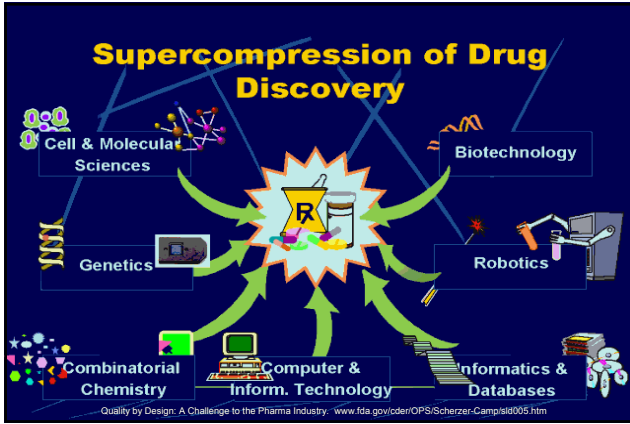
Product Life Cycle



Total Product Life Cycle. David W. Feigal, CDHR 2004

Traditional Drug Development





Analytical Lifecycle Deliverables

- Assure identity, purity, stability, safety, analysis/bioanalysis and quality of the product throughout its' lifetime
 - Package Label
 - CMC, PAT
 - Clinical / Bioanalysis
 - Quality
 - QbD Initiation
- Pre-IND, EOP2, Pre-NDA, CTD-Q, e-NDA, P4
- Sound Science
 - Good Scientific Practices / Principles
 - Good Documentation Procedures
- Common Lifecycle Thread is Analysis



Regulations - 21 CFR § 312

- The amount of information on a particular drug (or biologic) that must be submitted in an IND to assure the accomplishments of the objectives... *{safety & quality}* ...depends upon such factors as the novelty of the drug or biologic, the extent to which it has been studied previously, the known or suspected risks and the developmental phase of the drug or biologic."
 - [21 CFR § 312.22(b)]
- Although in each phase of the investigation sufficient information is required to be submitted to assure the proper identification, quality, purity, and strength of the investigational drug or biologic, the amount of information needed to make that assurance will vary with the phase of the investigation, the dosage form, and the amount of information otherwise available.
 - [21 CFR § 312.23 (a)(7)(i)]

cGMPs - Investigational Products

- Drugs and biologics including investigational products are required to be manufactured in accordance with cGMPs
 - If not, considered adulterated
 - [501(a)(2)(B) FD&CA]
 - Compliance with
 - 21 CFR § 210, 211 Current Good Manufacturing Practices for Finished Pharmaceuticals Regulations
 - 21 CFR § 600, 610 Biologics
 - Components, API, Finished Product
 - Source Material
 - Components
 - Manufacturing Process
 - Safety-related Process Controls/ Data
 - Analytical Methods/ Specifications
 - Stability

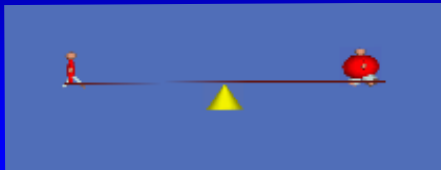
GxPs - Investigational Products

- Good Laboratory Practices (GLPs) (21 CFR part 58)
- Laboratory Requirements (42 CFR Ch. IV § 493)
- FDA Compliance Policy Guides
- College of American Pathology (CAP) Programs
- Clinical Laboratory Inspection Amendments
- United States Pharmacopoeia
- Others, etc.

IND ↔ NDA/ BLA / cGMP Balance

**CMC IND
Review**
[21 CFR § 312, 314,
GXP, etc.]

**cGMP
Inspection**
[21 CFR § 210, 211,
600, 610, etc.]



Early Phase Quality

- Personnel
- Quality Systems
- Facility and Equipment
- Control of Components
- Production and Documentation
- Laboratory Controls

Early Phase Quality

- Good Documentation Procedures
 - Defined written procedures
- Adequately qualified and controlled facility and equipment
- Accurate, consistent recording of data
 - Manufacturing and analysis

Early Phase Quality

- Controls tailored to the product, manufacturing process and facility
- cGMPs consistent with sound scientific methodology, product development and quality principles
 - cGMP are the minimum requirement
- Audit ready philosophy
- Risk Assessment - justify rationale and document
 - Utilize appropriate controls
- CROs/Outsourcing are subject to cGMP inspection

Early Analytical Methods

- Assure safety of the product
- Analytical link throughout product development lifecycle (and registration)
 - Acceptance criteria
 - Specification development
 - Reference standard (s)
 - Process development and validation

Early Analytical Methods

- Knowledge based approach
 - Incremental
 - Instrument /personnel qualification
 - Method qualification and evaluation
 - Validation
 - Documentation
- Methods should be reliable.
- Assurance of quality, identity, purity, strength, potency and stability.

Early Analytical Methods

- Limited API
 - Initial Considerations Non-destructive Techniques
- Basic Physical / (Bio) Chemical Characterization
- Qualified Instrumentation
 - Analytical Instrument Qualification (Bansal *et al.* 2004)
- Computer Assisted Simulations, Models
- Documentation
- Retains

Laboratory Controls

- Testing
 - Analytical tests used in production (e.g., testing of components, in-process material, packaging, drug product) should be scientifically sound (e.g., specific, sensitive, and accurate) and reproducible for the specified purpose.
 - Stability
 - Container Closure
 - Documentation

Analytical Methods Validation

“FDA recognizes that modifications to the method of preparation of the new drug or biologic substance and dosage forms...are likely as the investigation progresses” [21 CFR 312.23 (a)(7)(i)]

“As drug or biologic development proceeds ...the sponsor should submit information amendments to supplement the initial information submitted on the CMC with information appropriate to the expanded scope of the investigation.” [21 CFR 312.23 (a)(7)(ii)]

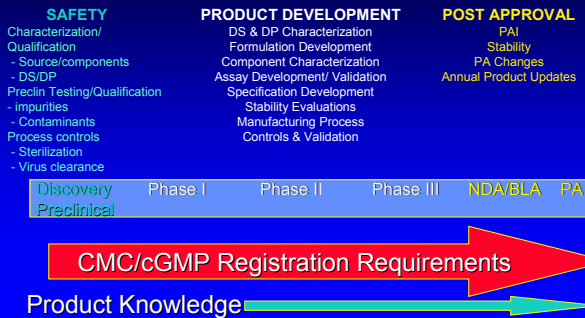
AR&D Methods and Validation Change Control

- Intended, unintended changes
- Evaluate the impact of the change(s) on the DS & DP product quality with regard to safety and efficacy
- IND information amendment
 - Manufacturing changes
 - Identify changes that are likely to affect safety and efficacy prior to use in clinical studies
 - Comparability study(s)
 - Other supporting studies and data
- Good Documentation Practices

Investigational Studies & cGMP

- May not always fully comply with cGMP regulations (i.e., 21 CFR § 211)
 - Initial manufacture, analysis
- cGMP regulations designed for post approval commercial manufacture
 - Defined product quality attributes
 - Established manufacturing process
- cGMPs principles are applicable to manufacture of investigational products
- Types and extent of control may differ due to type of product and stage of development

CMC/cGMP Development Lifecycle



Biologic CMC Requirements

- Cells, Viruses, Banking Systems
 - Origin / Method of collection
 - History
 - Manipulation, establishment of banks, cryopreservation
 - Testing – Source/ source material
 - (e.g., Microbiology, endogenous/ adventitious agents, (bovine/ porcine), identity, purity, activity, replication competent viruses, etc.)
- Genetic material
 - Origin
 - Gene modification, construction of vector, purification
 - Testing (e.g., sequencing)
- Evaluation
 - Risk assessment of parent cells
 - History, exposure to viral agents
 - Screening donors for risk factors, absence of disease markers
- Testing for viruses
 - Endogenous virus testing
 - Donors, animals, host cells, cell banks, product
 - General and Species specific tests
 - Approved / accepted tests (if available)
- Control
 - Establishing & maintaining cell banks, viral seeds under cGMP's
 - Establishing plasma donor deferral roles for unsuitable donors
 - Closed herds & flocks, sentinel animals
 - Quarantine until testing and control assures and establishes safety
- Stability

Biologic CMC Needs

- Component source, safety and quality
 - BSEs
 - Assure material from BSE-free country
 - The "List" [USDA 9 CFR § 94.18]
 - Maintain traceable records
 - Test for viral agents
 - Sterility
 - Cell Banks, Product, Placebos
 - Cell therapies
 - Mycoplasma
 - cultivable and non-cultivable
 - Endotoxins
 - Initial finished product specifications
 - Rapid Microbial Methods Development
 - Develop qualification program during development

Biologic CMC Needs Analytical Procedures

- Biological Substance & Biological Product
 - Appropriate analytical procedures
 - Description of tests
 - Analytical procedures
 - Acceptance criteria and specifications
 - USP <1041, 1043, 1045-1050, Others USP Chapters >
 - Appropriate analytical evaluations
 - source material, components, intermediates, in-process manufacturing, BS & BP, stability
 - Appropriate acceptance criteria may not be known for all materials and all tests
 - May have "report results"
 - Establish acceptance criteria for known (suspected) safety-related tests (e.g., source materials, components, lot release BS/BP)

CMC Needs – API & FP

- Active Pharmaceutical Ingredient & Finished Product
 - Full description of the drug substance
 - Identity, physical / chemical characteristics, stability
 - Method of synthesis (or isolation) and purification, including:
 - Appropriate selection of starting materials
 - Manufacturing process controls (quality controls)
 - Specifications (including test methods) necessary to ensure purity and drug product performance
 - Level and qualification of impurities
 - Container closure and stability information
- Placebos
- Complexity

CMC Needs – API & FP

- Specifications are the quality standards (i.e., tests, analytical procedures, & acceptance criteria) that ensure the quality and performance of the DS, DP, intermediates, raw materials, reagents, container closure systems, etc. that assure the product's safety and efficacy.
- Solid oral dosage forms should include:
 - Appearance
 - Assay/potency
 - In-vitro dissolution or disintegration test
 - Impurity profile
 - Content uniformity
 - Other critical quality attributes, as appropriate
 - USP monograph/public standards are considered minimum requirements
 - Additional specifications may be needed (e.g., impurities)

United States Pharmacopeia National Formulary

- The primary purpose is to provide authoritative standards and specifications for materials
- Whenever a medically significant difference in bioavailability has been found among supposedly identical articles, a dissolution test has discriminated among these articles.
 - There is no known medically significant bioequivalence problem with articles where 75% of an article is dissolved in water or acid at 37°C in 45 minutes in the official basket or paddle apparatus operated at the usual speed, that is, USP First Case.
- Medically significant cases of bioequivalence rest mainly on four causal factors:
 - inappropriate particle size of an active ingredient;
 - magnesium stearate in excess as a lubricant-gliadant;
 - coatings, especially shellac;
 - inadequate disintegrant.
- Each of these factors is reactive to dissolution testing.

CMC Needs – API & FP

- Stability Protocol
- Storage Conditions
 - Room temperature (RT) (25°C/60% RH)
 - Accelerated (40°C/75% RH)
 - Refrigerated (4-8°C)
 - Sub-zero (> -20°C)
- Tests & acceptance criteria
 - Stability indicating assay
 - Testing frequency
 - ICH

CMC Needs - Stability Studies

- Investigational product should be stable during planned duration of clinical studies
 - need to conduct stability in all phases [21 CFR § 312.23(a)(7)(ii)]
- Additional information to support stability
 - Knowledge of product class and stability
 - Unique, labile product, unknown product class
- Protocols
- Comparability throughout development
- Sufficient product retains

Laboratory

- Analysis and Testing
 - Specified quality / safety attributes monitored
 - Scientifically sound analytical procedures
 - Specificity, sensitivity, accuracy
 - Written procedures, controlled conditions
 - Calibration and maintenance of laboratory equipment
 - Initiate stability study to support use in clinical trials
 - Retains
 - Documentation

Quality

- Quality plan, systems, SOPs, Documentation
 - Review, release and approval of components, production procedures, analysis, acceptance criteria
 - Batch release
 - Product / process / analytical reviews
 - OOS observations, deviations and corrective actions
- Independence
- Appropriately trained personnel, equipment, procedures

Science Based Specifications

- Specifications to be based on:
 - Clinical Relevance
 - Safety Considerations
 - Process Capabilities
 - Product Development History and Knowledge
 - Development plans, protocols, reports
 - Integrated statistical approaches and methodologies
 - Risk-based assessment of early stage product
- Product quality assessment
- Quality Systems
- Sound scientific principles
- Manufacturing science, PAT
- Applicable guidances
 - ICH Q 5A-E, 6AB, 7, 8, 9 & 10, CDER/CBER Guidelines, USP
- Audit ready

ICH – Quality, FDA QSA

- Q1A-F Stability, Photostability, Data
- Q2A-B Validation of Analytical Procedures
- Q3A-C Impurities, Residual Solvents
- Q4B Regulatory Acceptance of Analytical Procedures and/or Acceptance Criteria
- Q5A-E Quality/Safety/ Comparability of Biotechnology Products
- Q6A-B Specifications
- Q7A Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients
- Q8 Pharmaceutical Development
- Q9 Quality Risk Management
- Q10 Pharmaceutical Quality System
- FDA, *Guidance for Industry, Quality Systems Approach to Pharmaceutical CGMP Regulations* (FDA, Rockville, MD, September 2006),

Objectives of ICH Q10

- The pharmaceutical quality system should:
 - Achieve product realization. The manufacturer seeks to consistently provide a **product of the quality** necessary to meet the requirements of patients, healthcare professionals, regulatory authorities, and internal customers.
 - Establish and maintain a **state of control**. This goal is met by using effective monitoring systems for process performance and product quality to provide assurance of continued suitability and capability of process.
 - Facilitate continual improvement by identifying and implementing necessary **product quality improvements, process improvements, variability reduction, innovations, and enhancements of the pharmaceutical quality system**, thereby increasing the ability to consistently fulfill quality requirements. Risk management techniques may be used to identify necessary areas for improvement.

Summary

- cGMPs apply throughout the product development lifecycle
 - Assess risks and take appropriate controls / actions
- Emphasize Product Quality
 - Quality by Design
 - Documentation, SOPs, Training, Qualification
- FDA Guidelines, ICH, USP
- Know Thy Product
 - Development / Product Lifecycle
 - Product / CMC Development Plan

Questions / Comments ?