INTEGRATED DRUG DEVELOPMENT PROCESS
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- Developability Assessment Supporting Drug Candidate Selection
  - Profiling of key Physicochemical Properties
  - Biopharmaceutical Assessment

- Preformulation
  - Solubility, Stability, Dissolution Rate and Solid State Properties
  - Salt and Form Screening and Selection
  - Excipient Compatibility

- Dosage Form Design
  - Conventional
  - Non-Conventional

- Formulation Development, Evaluation and Scale-up

- Equipment and Processing

- Regulatory Considerations
REGULATORY CONSIDERATIONS
Main Regulatory Bodies – Global Drug Product Development

- Food and Drug Administration
- European Agency for Evaluation of Medicinal Products (EMEA) & Individual Countries Regulatory Agencies in Europe
- Japanese Regulatory Agency
- Rest of the World – Individual Countries Regulatory Agencies
REGULATORY CONSIDERATIONS
Main Areas of Contact - FDA

- Guidelines, Federal Register (cGMPs)
- FDA Reviews
  - eIND (exploratory IND)
  - IND (Investigational New Drug application)
  - End of Phase 2 Meeting (Briefing Book)
  - NDA (New Drug Application), ANDA (Abbreviated NDA), Supplements
  - Questions
- FDA Inspector
  - GMPs Inspections
  - Pre-Approval Inspections
  - Validation
REGULATORY CONSIDERATIONS
Validation - Many Concurrent Activities (Tech. Transfer)

- Scale-up of Unit Processes (10x)
- Site Transfer to Production Facilities
- Validation of Manufacturing Process
- Support for Pre-Approval Inspection
REGULATORY CONSIDERATIONS
Production Work Environment

- Experience is beneficial
- GMPs Paramount
- High Visibility/Stressful - Delays Counted in Lost Revenues of New Product
- Speed in Decision Making is essential
- Teamwork/Communication
REGULATORY CONSIDERATIONS
Validation - Historical Perspective

- Release Specifications and In-Process Controls
- Validation (Sterile Procedures)
  Assurance that each Unit Operation does what it purports to do – Robust Processes
  Mixing, Granulating, etc.
- PAT (Process and Analytical Technology) Initiative – Quality by Design – Critical Path Initiative – CRADA (Cooperative Research And Development Agreement)
REGULATORY CONSIDERATIONS

Validation Process

• Documentation Intensive Program
  Protocols
  Acceptance Criteria
  Reports

• Validate (3 sequential production scale batches)

Control Critical Parameters
  Batch Records
  SOPs
  In-Process Controls
  Specifications
REGULATORY CONSIDERATIONS
Validation Process

• Establish cGMPs in the Production Environment
  Validation Master Plan
  • SOPs
  • IQ, OQ, PQ, etc.
  • Training
• Write Protocol and Master & Batch Record
  Acceptance Criteria
  Approvals
REGULATORY CONSIDERATIONS

Validation Process

- Manufacture Successfully Three Sequential Production Scale Batches
- Extensive Unit Operation Testing
- Product Release Testing
- Packaging Testing
- Stability Report
- Validation Report
- Approvals
REGULATORY CONSIDERATIONS
Validation Process

- Blend Uniformity
- Weight Uniformity, Function of Speed (Beginning, Middle, End)
- Stability of Intermediate Steps (Holding Time)
- Hardness, Thickness, Disintegration Time, Dissolution (Beginning, Middle, End)
- Hardness, Thickness, Disintegration Time, Dissolution, Friability (Compression Force)
- Content Uniformity (Beginning, Middle, End)
- Release Testing
REGULATORY CONSIDERATIONS
Pre-Approval Inspection

- Mock PAI conducted by Corp. QA
- PAI conducted by Worldwide Regulatory Agencies
  Form 483 Observations ("483")
  Approvable
  Nonapprovable
REGULATORY CONSIDERATIONS
PAT Initiative - FDA

The use of modern process analytical tools and concepts in the pharmaceutical manufacturing to reduce process variability and manufacturing cost and at the same time improve the consistency of product quality.

- The concept is supported by the US FDA to further develop cGMP to a more science and risk based approach to product quality regulations incorporating an integrated quality system approach.
<table>
<thead>
<tr>
<th>Problem</th>
<th>Regulated Pharmaceutical industry manufacturing</th>
<th>HIGHLY regulated</th>
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<tbody>
<tr>
<td></td>
<td>Cost of GMP compliance</td>
<td>high</td>
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<tr>
<td></td>
<td>Despite this: process efficiency &amp; effectiveness</td>
<td>low (high wastage &amp; rework); level of technology not cutting-edge</td>
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Problem: for Regulators

- Resource intensive oversight
- Expensive and time-consuming litigation and legal actions
- Need to deal with recalls and shortages of medically necessary drugs
Problem: for Industry

- Culture: antithesis of continuous improvement
- Regulatory burden: high and costly, but not viewed as contributing to better science
- Consequences of noncompliance: potentially catastrophic
Problem: for Public

- Cost of drugs viewed as very high
- Hostility towards pharmaceutical industry
- Fear of changes portrayed as deregulatory
PAT as Exemplar of New Initiative

- Process being used to facilitate PAT can be a model for introducing new technologies.
- Focus on science makes change acceptable to most parties.
- Findings on PAT can be extrapolated to other problem areas.
What do we hope to accomplish?

- Optimize product/process quality
- Allow for continuous improvement
- Promote use of up-to-date science
- "Right-size" regulatory burden
- Effectively and efficiently utilize FDA resources
- Demonstrate adoption of new technologies by industrial sector
- Maintain public confidence
REGULATORY CONSIDERATIONS
PAT Initiative - Scheme

PROCESS

PROCESS ANALYTICAL TECHNOLOGY (PAT)

Control

PROCESS CONTROL SYSTEM (PCS)

Analysis

Automatic

On-line Feedback
REGULATORY CONSIDERATIONS
PAT Initiative - Example

FILLING of VIALS

CHECKING WEIGHT of EACH VIAL

READJUSTMENT of DOSING DEVICE

Control

Analysis

Feedback
REGULATORY CONSIDERATIONS

PAT Initiative - FDA

- **Methodology**: Near Infrared on-line spectroscopy (NIR)
- **Key Results**: On-line measurement of concentration of drug and isomer in toluene solution to determine endpoint of evaporation.
- **Breakthroughs**: 1. Improved process robustness
  2. Increase of step yield (≥ 5%)
  3. Decrease time cycle to 24 h
  4. Elimination of In Process Control
REGULATORY CONSIDERATIONS - PAT Initiative - FDA

- FTIR
  - unstable intermediates
  - concentrations
  - end point of reaction
  - eventual formation of unstable intermediates

- Raman
  - concentrations
  - end point of reaction
  - eventual formation of unstable intermediates

- Reaction calorimeter
  - heat release rate
  - data for development
  - safety data