Technology Transfer
A Quality Systems Approach
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Objectives:

- Better understanding of the scientific basis and process fundamentals to technology transfer
- Improve information exchange and integration across departments
- A Quality Systems approach to reducing regulatory problems and avoid common pitfalls
- Improve performance of implementation and timelines
Objectives:

- Better understanding of validation issues
- Current CGMP and international requirements
- Partnership with Quality Assurance
- Technology transfer viewed as a process continuum
What is technology transfer?

- Process of transferring knowledge about how to produce a specific drug from discovery research to process scale up, to full scale size in manufacturing, to FDA licensing, and commercial launch of the product into the market place.
History

- Drive to be first to market
- Failure can cost millions of $
- Delay in availability of life saving drugs
- Loss of stock equity
- Bankruptcy of companies
- Loss of jobs
Regulator Expectations

- FDA-CDER Risk Based Approach
- Risk Assessment
- Process Analytical Technology (PAT)
- CGMPS for the 21st Century
- Several new FDA Guides
- New EC rules for Medicinal Products
- ICH Q8, Q9 and Q10
Differences between Quality System and CGMPs

- Quality Management
- Quality Assurance
- Quality Risk Analysis
- Preventive Actions
- Risk Management
- Continuous Improvement

(An FDA Perspective on QS, R. Sausville, PDA/FDA, 2005)
Quality System – Clinical Development

- Management needs to support QS
- QS needs to be in-place for investigational drugs
- Design by Quality
“...the agency is looking for a clear and consistent way of distinguishing between those manufacturers who rely on chance or art to develop their products and those that put significant efforts into designing experiments, etc.” (F-D-C Reports 2003, pg 2.)
CGMPs for 21st Century

- FDA intends on using the following principles:
  - Risk based orientation
  - Science based policies and standards
Real Life

- Estimated cost to bring new drug to market is $500 to $800 million
- Requires 10-15 years of time
- Only 1 of 200 discovered drugs ever get to market
- Estimated 7 of every 10 products do not return capital investment to their company
What This Means

- Critical to become more efficient and effective to develop new products
- Must utilize research findings and translate into commercial innovation
- Must improve application of “upstream” scientific knowledge
- “Downstream” activities of new product design
- Ineffective technology transfer delays can cost $1- $3 million lost per day in sales
Practices

- The field is exploding with articles, publications, and newspaper stories
- Lack of any scientific or experimental data
- Few technology transfer models
- Lack of company polices
- Lack of measurements
Research Study

- Team Communication
- Leadership
- Team Structure
Research Method

- A 50 point questionnaire was developed
- Survey of 15 different company experts
- ANOVA Analysis
- Generated data on input variables
- Each question decomposed into 5 multiple variables
- Several published case studies were compared to statistical results
Research Study Variables

- Cross-functional
- Chain of Command
- Formal Structure
- Data Sharing
- Formal Procedures
- Effective communication
Study Results

1. 12 of the 15 companies surveyed Did Not provide any training to their technology transfer teams.

2. One third of the companies Did Not have a defined team leader.

3. 12 companies Did Not have full time membership on the Tech. Transfer team.
Study Results

4. Most companies use cross-functional teams.
5. Successful teams have defined goals.
6. Written SOPs on the process are critical.
7. Important to have central data base.
8. Several companies reported that their team leader was not highly motivated.
Key Factors for Successful Tech. Transfer Team

1. Effective Communication
2. Strong Leadership & mgt. commitment
3. Quality Policy & Quality Plan
4. Training
5. Cross-functional Team
6. Clear Team Goals
7. Technology Transfer Procedures
A Case Study on the Transfer of a Lyophilized Product

by

Frank S. Kohn, PhD
Goals

- Optimize the technology transfer process
- Use Quality System approach (ICH Q10)
- Use various quality tools (RA & PAT)
- Focus on the lyophilized process
Case Study Background

- USA mfg. of a lyophilized product
- Transfer product to mfg. in Europe
- Reduce transfer timeline
- Use RA(ICH Q9) & PAT tools
- Optimize technology transfer process
ICH Q9 – Risk Analysis Process

- RMP (Risk Mgr. Tools)
  - Risk Mgr. Process
    - Risk Assessment
      - Risk Control
        - Risk Communication
          - Risk Review
Risk Assessment

- What can go wrong?
- What is probability?
- What are the consequences?
Risk Identification

- Historic process
- Informed opinions
- Possible consequences
Risk Analysis/Evaluation

- Identify hazards
- Ask follow up questions
- Ability to detect risk
- Numerical scale (0-10)
- Descriptors (High, Medium, Low)
Risk Control/Reduction

- Is risk acceptable?
- Can we reduce, eliminate risk?
- Is it practical?
- Is new risk introduced?
**Formal Risk Assessment**

- Document existing controls
- Documented scientific rational
- Mfg. step prior to lyophilization
- Mfg. steps after lyophilization
- Potential contamination issues
Failure Mode Effects Analysis (FMEA) Ref. ICH-Q9

- Evaluates potential failure of process
- Predicts the effect on outcomes
- Identifies source of failure
- Eliminate, reduce or control failure
- Requires process/product understanding
## FMEA example of single process

<table>
<thead>
<tr>
<th>RA #</th>
<th>Step</th>
<th>FA Mode</th>
<th>Cause</th>
<th>Control</th>
<th>Prob.</th>
<th>Dect./ Found</th>
<th>RV</th>
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<tbody>
<tr>
<td>1</td>
<td>Manual loading</td>
<td>Contavials</td>
<td>Env. expose</td>
<td>ISO5</td>
<td>SS lid</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Person contact</td>
<td></td>
<td>Gowns/gloves</td>
<td>EMC Gloves Cult.</td>
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<tr>
<td>3</td>
<td>Ergo/Handle</td>
<td></td>
<td>Sterile SS lid Autocl.</td>
<td>Check Cycle Media fills</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Process Analytical Technology

- PAT combined with Risk Analysis:
  - Select and map a process step
  - Conduct Risk Analysis
  - Evaluate existing process
  - Collect sufficient data
  - Process Model & Gap Analysis
Operation of the Lyophilizer
FREEZE DRYER LOADING AUTOMATION

- Minimize particulates
- Maintain laminar air flow
- Reduced operator handling
- Reduces microbial contamination
- Reduces tray cover sterilization
Evaluated Other Lyo. Parameters

- PC optimization programs
- Evaluated:
  - MTR (mass transfer resistance)
  - Rate of sublimation
  - Shelf temp. control
  - Heat transfer of product
  - Optimal lyo cycle
  - CIP/SIP
Optimizing the Cycle

- Freezing can have a significant impact on primary drying characteristics.

- Increase rate of sublimation leads to lower product temperature because of the enthalpy of ice sublimation.
CIP/SIP of the Freeze Dryer

- Clean in Place are critical system in freeze dryers.
- In the past CIP systems in freeze dryer have cause difficulty in product residue removal.
- Steam in Place are critical to microbial control in a freeze dryer.
Manufacturing Process

- Final Blend
- Filling
- Loading
- F/D
  - Unload
    - Inspect
Example Lyophilizer
Actions that Reduced Risk & Implemented PAT

- Automation of tray loading
- Reduced loading time
  -(9 hrs. to 7 hrs.)
- Eliminated personnel handling
- Enhanced algorithms in computer controls
- Optimized freeze drying cycle
  -(72 hrs to 58 hrs) or 20% reduction in cycle
Lessons Learned

- Principles of Quality Risk Management are directly applicable to technology transfer model
- The element of risk should be minimized or eliminated
- The level of automation and real time quality can provide additional benefits to the technology transfer process
- Communication and training of the technology transfer team are critical for success
Lessons Learned - Defined drug process

- Process flow diagrams (Quality by Design)
- Facilities requirements (Contamination)
- Process requirements (Process Capability)
- Equipment requirements (Validation)
- Engineering requirements (GEP)
- Maintenance requirements (Cert.)
- Environmental requirements (Reg.)
- Safety requirements (OSHA, etc.)
Define Drug Process

- Product “hold” points
- Utilities & facility requirements
- Facility site selection
- Product specifications based on Science
- Chemical & Reagent list
  
  Include Certification of Analysis

Certified Vendor
Define Drug Process

- Stability indicating assays
- Product description
- Documentation
- Process transfer
- Assay transfer
- Validation

Key critical process parameters
Cleaning validation
Laboratory Activity Report

- State purpose
- Establish responsibilities
- Define terminology
- Establish experimental design
- Identify factors for acceptance
  - Specificity
- Limits of detection
Laboratory Activity Report

- Verify SOPs
- Verify training
- Establish data retention requirements
- Describe reporting formats
- Identify content of reports
QS Technology Transfer Plan

- State purpose
- Define scope
- Establish responsibilities
- Define terminology
- Summarize planned activities
- Establish record keeping
- ID sequences, linkages and interdependencies
Project Plans

- Summary R&D and Scale-up activities
- Assign responsibilities
- Define raw materials
- Establish specifications
- Define production & control facilities
- Establish formulation & production processes
Project Plans

- Develop cleaning methods
- Implement validation
- Identify requirements for regulatory filing
- Identify training needs
- Identify content of development reports
Project Plans

- Determine processes to validate
- Define analytical methods
- Establish document retention
- Develop stability protocols
- Follow change control SOPs
- Establish reprocessing methods
Common Problems in TT

- Insufficient data to completely understand process
- No Risk analysis performed
- Capital investment needs ID too late
- Passing the problem “over the fence”
- Data dumping
- Failure to analyze the data
Key Success QS Factors

- Technology Transfer Team
- Project Management Plan
- Defined Metrics/Goals/Timelines/Responsibilities
- Scientific evaluation of your processes
- “Risk Analysis” of product/process
- Utilize “current & new technology”
Key QS Success Factors

- Get regulatory agencies involved
- Develop production and marketing schedules
- Good Documentation Practices
- Change management system
- CAPA system
- Quality “feed back” program
**Key QS Success Factors**

- Self-assessment process including audits
- External assessment such as customer audits
- Quality Management review system
- Dissemination of knowledge
QUESTIONS?