New Product Assessment In A Multiproduct Environment – A Risk-based Approach

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Presentation Overview

- Cook Pharmica Overview
- Multiproduct Processing
- New Product Assessment
Objectives

- Understand how new products are introduced into a multiproduct facility through an effective cross-functional evaluation process
- Utilize risk assessment to conclude acceptability and identify appropriate control measures
- Understand the requirements for communication to Regulatory Agencies
Cook Pharmica

- Contract development and manufacturing organization
- Wholly-owned subsidiary of Cook Medical
- Legacy of life sciences innovation since 1963
Cook Pharmica Campus

Building A
450,000 square feet

Building B
450,000 square feet
Cook Pharmica Operations

Drug Substances Manufacturing
Drug Product Manufacturing
Medical Device Manufacturing
Support Services
A **product** is defined as material with a given active pharmaceutical ingredient, dosage level, formulation, and/or packaging configuration. If any of these attributes change, the material is considered to be a different product.

Control is essential to minimize cross-contamination or co-mingling between products.
Multiproduct Processing Controls

- Operational Flows
- Time
- Physical Containment
- Cleaning
- Documentation
- Personnel
- Risk Assessment & Mitigation
Multiproduct Processing Controls

Operational Flows
- Product
- Personnel
- Material
- Equipment
- Waste
Multiproduct Processing Controls

Operational Flows

- Transition strategy
Multiproduct Processing Controls

Time
- Campaigning
- Open vs Closed processing
Physical Containment

- HVAC envelopes
- Segregated critical utilities
- Closed systems
- Physical separation
- Disposable technology
Multiproduct Processing Controls

Cleaning
- Sanitization
- Waste removal procedures
- Line clearance / changeover
- Cleaning verification/validation
- Dedicated equipment
- Single-use disposable systems
Multiproduct Processing Controls

Documentation
- Status tagging
- Client project coding
- Unique lot numbering
- Color coded batch documentation
Multiproduct Processing Controls

Personnel
- Training
- Verification
- Oversight
Multiproduct Processing Controls

Risk Assessment & Mitigation
- New Product Introduction
- Technical Transfer risk assessment
- Process Failure Mode and Effects Analysis
- Equipment Failure Mode and Effects Analysis
- Change Control risk assessment
New Product Introduction Process

- New Product Evaluation
- New Product Assessment
- Management Approval & Communication
New Product Introduction

Risk Management
New Product Introduction

Risk Management = Good Decision Making
New Product Evaluation

- Initial Business Development meeting with Quality, Operations, EHS, Technical Reviewers
- Request for Proposal and client supplied information
- If possible…
  - Cook Pharmica Product Survey (completed by Client)
  - Cook Pharmica EHS Questionnaire (completed by Client)

Go / No-go to submit Proposal
New Product Assessment

- Occurs prior to introducing new product into manufacturing area
- Incorporates risk management principles
- Is a business driven process
- Utilizes internal and external subject matter experts
- Integrated with the multiproduct control strategy at Cook Pharmica
New Product Assessment

New Product Assessment

GMP/Regulatory (Risk to Product)

Health & Hygiene (Risk to Worker)

Facility (Risk to Cook Operations)
New Product Assessment

Manufacturing

Technical Services

Cleaning Validation

QA

Process Validation

QC

Process Development

EHS

Hygienist

Toxicologist

Regulatory
New Product Assessment

Necessary Information for NPA:

- Project proposal and technical documents (e.g., PFD)
- Cook Pharmica Product Survey (completed by Client)
- Cook Pharmica EHS Questionnaire (completed by Client)

- Hazard Information
  - Control banding category
  - Occupational Exposure Limit (OEL) – mass per cubic meter of air
  - Acceptable Daily Exposure (ADE) – mg/day

- Cleaning Validation Assessment Plan and acceptance criteria based upon recovery studies
Cleaning Methodology

1) Determine the most appropriate cleaning procedure for the equipment:
   Generate acceptance criteria data for the product
   The cleaning method will be determined by the process, the equipment, the cleaning agents and the cleaning techniques available
   All aspects of the cleaning are clearly defined in SOP’s be it manual, CIP, or COP

2) Develop and validate the sampling and chosen analytical methods for the compound(s) being cleaned.
   1. Swab
   2. Rinse
   (determine % recovery, limit of detection, limit of quantitation, accuracy of method, reproducibility, etc.)
Cleaning Methodology

3) Evaluate equipment surfaces and determine
   Equipment surface area (necessary to calculate carryover into subsequent batches)
   Worst case locations to sample (swab sampling)
   Volume and type of rinse to be employed (rinse sampling)
Cleaning Methodology

- ISPE baseline guide Risk-MaPP vies for improving the scientific approach for establishing limits with Safe Threshold Value (STV) calculated from ADE data versus standard traditional Maximum Allowable Carryover calculations

- Appropriate for highly hazardous actives
- Need for reducing variability in deriving acceptable exposure limits thereby ensuring consistency
New Product Assessment

GMP/Regulatory Factors:

- Is there a specific requirement to handle the product in a dedicated facility?

Examples:

- Beta-lactam antibiotics including penicillins, cephalosporins, penems, carbacephems, and monobactams
- Animal health products with no human safety data
New Product Assessment

GMP/Regulatory Factors:

- Can cleaning be carried out to meet the required criteria?
  
  Answer is typically YES with supporting data
  
  - Product properties are assessed by Technical Services and Cleaning Validation laboratory studies
New Product Assessment

GMP/Regulatory Factors:

- Can cleaning be carried out to meet the required criteria?
  
  Answer is typically **YES** with supporting data
  
  - Product properties are assessed by Technical Services and Cleaning Validation laboratory studies

If **NO**…

- Requires evaluation of the stage of the process and ability to isolate equipment to prevent cross-contamination (e.g., use of disposable technology)
New Product Assessment

GMP/Regulatory Factors:

- Are procedures, controls, and facility designed to avoid mix-ups?
  
  Answer is typically **YES**

- Project specific requirements are assessed by Functional Areas to identify any unique attributes which may impact current multiproduct processing controls (e.g., location of purification equipment needed for the process)
New Product Assessment

GMP/Regulatory Factors:

- Are procedures, controls, and facility designed to avoid mix-ups?
  Answer is typically **YES**
  - Project specific requirements are assessed by Functional Areas to identify any unique attributes which may impact current multiproduct processing controls (e.g., location of purification equipment needed for the process)

If **NO**…

- Can procedures, controls or design elements be introduced to prevent mix up?
New Product Assessment

GMP/Regulatory Factors:

- Is the potential for mechanical or airborne transfer controlled to a safe pre-determined level?
  
  Answer is typically **YES**

- Project specific requirements are assessed by Functional Areas
New Product Assessment

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- Is the potential for mechanical or airborne transfer controlled to a safe pre-determined level?
  
  Answer is typically **YES**
  
  - Project specific requirements are assessed by Functional Areas

If **NO**…

- Can modifications or procedures be put in place to control mechanical or airborne transfer to safe pre-determined levels? (e.g., need for raw material satellite samples, formulation activity requiring isolation unit, dedicated equipment)
New Product Assessment

GMP/Regulatory Outputs:

- Single product facility
- Multi product facility with no restrictions
- Multi product facility with dedicated or disposable equipment for process step or procedural control
New Product Assessment

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Hazard Information

- Control banding category
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- Cleaning Validation Assessment Plan and acceptance criteria
New Product Assessment

Health & Hygiene Factors:

Assess Exposure Potential

- Who is at risk?
- Frequency?
- Process factors that might influence exposure? (e.g., open or closed process, raw material/intermediate)
- Pathway for exposure?
New Product Assessment

Health & Hygiene Factors:

- Are the exposures adequately controlled?
  If **YES**…
  - Use standard PPE and control systems
New Product Assessment

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- Are the exposures adequately controlled?
  - If YES…
    - Use standard PPE and control systems
  - If NO…
    - Determine exposure control approach
New Product Assessment

Health & Hygiene Factors:

- Can the exposure be mitigated through change in material, process modification or equipment selection?
  
  If YES…

- Eliminate, substitute, or contain at source as appropriate
New Product Assessment

Health & Hygiene Factors:

- Can the exposure be mitigated through change in material, process modification or equipment selection?
  
  If YES…
  - Eliminate, substitute, or contain at source as appropriate
  
  If NO…
  - Evaluate appropriate engineering controls to reduce exposure
New Product Assessment

Health & Hygiene Factors:

- Following engineering controls to reduce exposure is exposure risk still too high?
New Product Assessment

Health & Hygiene Outputs:

- Determine Exposure Control Approach
- Eliminate Material
- Change Process
- Engineering Controls
- Personal Protective Equipment (PPE)
- Secondary Systems
- Tertiary Systems
New Product Assessment

Cook Pharmica Facility Factors:

- Does the process fit within our current acceptable product matrix, equipment, and resource capabilities?
New Product Assessment

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- Does the process fit within our current acceptable product matrix, equipment, and resource capabilities?
  
  If NO…

- Can we add or modify process capabilities, equipment and/or resources, subcontract, or provide referral?
New Product Assessment

Cook Pharmica Facility Factors:

- Are there any other considerations with potential impact to Cook and/or current Clients?

Examples:
- GDUFA facility fees
- Quality Agreement commitments
- Import / Export registrations
- DEA registration status changes
- ISO certifications
- USDA permit
New Product Assessment

Cook Pharmica Facility Outputs:

- Reject / Accept product introduction
- Expand facility capabilities
- Expand regulatory capabilities
- Change control
- Client notification and support client regulatory activity, if necessary
Methodology

Qualitative Risk Assessment

- Low Risk
- Medium Risk
- High Risk

NPA Departmental Risk Assessment Template

- Provides pre-determined questions and evaluation criteria for each department
- Includes functional area acceptability determination

NPA Departmental Risk Assessment Template:

- Provides pre-determined questions and evaluation criteria for each department
- Includes functional area acceptability determination
Management Approval & Communication

- Acceptability determination performed by VP of Quality
- Control plan actions identified
- Project scope for implementation
- Client Notifications
Communication

- Business Development
- Project Management
- Clients  ➞  Regulatory Authorities
- Regulatory Authorities
Regulatory Communication

- FDA Approved BLA Submissions
  - Supplement Changes Being Effected in 30 days (CBE-30) (21 CFR 601.12)
    “Manufacture of an additional product in a previously approved multiple product manufacturing area using the same equipment and/or personnel, if there have been no changes to the approved and validated cleaning and changeover procedures and there are no additional containment requirements.”
  - Sponsor is required to maintain a list of shared products in accordance with the CTD format for Biotech products (ICH M4Q)
  - Comparability Protocol
FDA Approved NDA/ANDA Submissions

- Sponsor is required to maintain a list of shared products in accordance with the CTD format for Biotech products (ICH M4Q)

Annual Reportable

Guidance for Industry CMC Postapproval Manufacturing Changes Reportable in Annual Reports June 2010 Draft Guidance

“2.3 Manufacture of an additional drug product (including investigational or developmental products) in an approved multiple-product area that is producing another product(s) if:

2.3.1 specific identity tests exist to differentiate between all products manufactured at the facility; and

2.3.2 a change-over procedure between manufacturing processes is established; and

2.3.3 the products do not represent an additional level of risk. Additional levels of risk might include, but are not limited to, the manufacture of highly toxic or potent products, highly immunogenic or allergenic products (e.g., penicillin), products that can accelerate degradation of another product (e.g., enzymes), products that represent a new or added risk for adventitious agents, or a product for adults added to a line manufacturing pediatric products.”
Regulatory Communication

- European Union
  - Sponsor is required to maintain a list of shared products in accordance with the CTD format for Biotech products (ICH M4Q)

- Health Canada
  - Annual Notification

Questions regarding whether a specific change requires a supplement or may be included in the annual report should be directed to the appropriate review division.
Questions?
References

21 CFR Part 211.42(c)

21 CFR 601.12

21 CFR 314.70


FDA Guidance for Industry: Non-Penicillin Beta-Lactam Drugs: A CGMP Framework for Preventing Cross-Contamination April 2013

Joint Technical Note DFIP/SDA/MAPA – GGIMP/ANVISA/MS Need for segregated facilities to manufacture drugs for veterinary use and for human use. Issued April 23, 2012

ICH Q9 Quality Risk Management

FDA Guidance for Industry Changes to an Approved Application: Biological Products July 1997

FDA Guidance for Industry Changes to an Approved NDA or ANDA April 2004

FDA Guidance for Industry CMC Postapproval Manufacturing Changes Reportable in Annual Reports June 2010 Draft guidance

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