COLLABORATIVE THINKING BUILDS ROBUST QUALITY

Developing Combination Products

Donald Singer
AGENDA

❖ Combination Products
❖ Contamination Control
❖ Scope
❖ Responsibilities
❖ Resources and Valuable Information
❖ Focus on Quality Relationships
COMBINATION PRODUCTS

Under 21 CFR 3.2(e), a combination product includes:

1. A product comprised of two or more regulated components, i.e., drug/device, biologic/device, drug/biologic, or drug/device/biologic, that are physically, chemically, or otherwise combined or mixed and produced as a single entity (such as a prefilled syringe or drug-eluting stent).

2. Two or more separate products packaged together in a single package or as a unit and comprised of drug and device products, device and biological products, or biological and drug products (a “co-packaged” combination product).

3. A drug, device, or biological product packaged separately that according to its investigational plan or proposed labeling is intended for use only with an approved, individually specified drug, device, or biological product where both are required to achieve the intended use, indication, or effect and where upon approval of the proposed product the labeling of the approved product would need to be changed.

4. Any investigational drug, device, or biological product packaged separately that according to its proposed labeling is for use only with another individually specified investigational drug, device, or biological product where both are required to achieve the intended use, indication, or effect (another type of crosslabeled combination product).
COMBINATION PRODUCTS

In practice, (REALITY !)

Almost every sterile drug meets a delivery device when being administered to a patient.

**Scope** – A drug-device combination, e.g. pre-filled syringe with an autoinjector, containing a pharma or biopharma drug

This is an R&D perspective for a new drug in development
CONTAMINATION CONTROL
Six Sigma Approach
Risk Assessment for Quality
QUALITY CONTROL INPUTS – NON-STERILE

Nonsterile Product Microbial Influences

- Facility Design & Maintenance
- Personnel Flow
- Equipment Design
- HVAC
- Storage Conditions
- Personnel Practices & Training
- Equipment Cleaning & Maintenance
- Manufacturing & Filling Processes
- Active Pharmaceutical Ingredients
- Raw Materials
- Primary Packaging Components

In-Process Materials

- Process & Cleaning Water
- Facility Housekeeping / Sanitization
- Nonproduct Contact Equipment
- Validation
- Product & Material Flow
- Personnel Gowns & Hygiene

Products
A STEERILE PRODUCT PERSPECTIVE

Sterility Assurance

- Sterility by Design

Selection of Production Method

- Aseptic Processing
  - Closed Systems
  - BFS/FFS
  - RABS
  - Media Fills
  - Isolators
  - Manned Cleanrooms

- Terminal Sterilization
  - <1222> Parametric Release
  - Low Temp / Low Dose

Facilities

- Controls
- Design Principles
- Environment

Procedures

- Interventions
- Facility / Equipment Treatment
- Compounding

Personnel

- Gowning
- Aseptic Technique
- Training

Sterilization

- <1228>

Depyrogenation

- <1228>

Monitoring

- Class vs. Monitor
- Trends
- Sample Methods
- Sample Site Selection

Raw Materials

- Sampling & <1229.3>
- <61> & <1111>

Primary Packaging

- Sampling & <1229.3>
- <61> & <1111>

Sanitize

- Facility / Equipment Treatment
- Airlocks / Passageways
- <107>

Equipment

- Sterilization / Depyrogenation
- Sanitary Design
- Closed Systems
- Single Use
CONTAMINATION PREVENTION

Who has responsibility?

Drug developer – risk assessment of final product and device combination for patient use

Device developer – risk assessment of life cycle of device through to patient use
ROAD MAP TO SUPPLIER MANAGEMENT

Identification of need

Planning

Selection

Evaluation

Final decision

Yes

No

Implementation of controls

Sustaining, monitoring, and feedback

End of relationship

What is the need to be fulfilled?

Defining the scope
Identification of requirements and expectations

Review of current suppliers
Investigating other potential suppliers
Desktop assessments

On-site/desktop assessment
Comparison of all suppliers
Decision made
Onboarding supplier

Receiving inspection

Metrics
Report cards
Business reviews

Intervention with supplier
Contingency and exit strategies

Project charter
Business need and selection requirements
Risk identification and assessment

Evaluation report of evaluated suppliers based on selection requirements
Risk assessment completed and controls identified
Request for quotes
Non-disclosure agreements
Draft control plan created for receiving and supplier

Audit report and recommendation
New supplier package
—add to MRP
—add to ASL with category and commodities
—submit required information to finance
Quality agreement approved

First article inspection approved
Control plan finalized for receiving and supplier (including MSA and Gage R&R)
Working toward shifting from F1 to supplier data to DTB or reduced inspection levels
Audits scheduled based on performance and risk, assigned by geographic location
and available resources
Supplier corrective action requests as required
Deviations and waivers

Performance reports—quality and delivery
Corrective action feedback
Recognition program
Face-to-face meetings
Total cost of ownership analysis completed

Total cost of ownership implemented
End of product life-cycle or project
Performance issues
Contingency plans and exit strategies implemented

J. Shore and J. Freije, 2016
ROAD MAP TO SUPPLIER MANAGEMENT

Process

Identification of need

Planning

Selection

Evaluation

Final decision

No

Process activities

What is the need to be fulfilled?

Defining the scope
Identification of requirements and expectations

Review of current suppliers
Investigating other potential suppliers
Desktop assessments

On-site/desktop assessment
Comparison of all suppliers
Decision made
Onboarding supplier

Receiving inspection

Metros
Report cards
Business reviews

Intervention with supplier
Contingency and exit strategies

Deliverables

Project charter
Business needs and selection requirements
Risk identification and assessment

Evaluation report of evaluated suppliers based on selection requirements
Risk assessment completed and controls identified
Request for quotes
Non-disclosure agreements
Draft control plan created for receiving and supplier

Audit report and recommendation
New supplier package
—add to MRP
—add to ASL with category and commodities
—submit required information to finance
Quality agreement approved

First article inspection approved
Control plan finalized for receiving and supplier (including MSA and Gage R&R)
Working toward shifting from RI to supplier data to DTS or reduced inspection levels
Audits scheduled based on performance and risk, assigned by geographic location
and available resources
Supplier corrective action requests as required
Deviations and waivers

Performance reports—quality and delivery
Corrective action feedback
Recognition program
Face-to-face meetings
Total cost of ownership analysis completed

Total cost of ownership implemented
End of product life-cycle or project
Performance issues
Contingency plans and exit strategies implemented

Database

J. Shore and J. Freije, 2016
VALUE OF CRITICAL INFORMATION

Information

Application

Experience

Understanding

Knowledge
SOURCES OF CRITICAL INFORMATION

❖ Specifications

❖ Product registration information

❖ Process map

❖ Physician/clinician feedback or panel evaluation

❖ Clinical trials
WHAT IS RELEVANT TO MICROBIOLOGICAL CONTAMINATION CONTROL?
SPECIFICATIONS

Be able to evaluate and distinguish safety and purity from efficacy/performance

Drug specs: (impact, assess for device integrity or drug stability)

Device specs: (impact, assess for drug compatibility or patient safety)
REGISTRATION INFORMATION

Drug information: e.g. protein, or small molecule, or oligonucleotide, or liposomal, or somatic cell
Also consider form: liquid or lyophilized
Consider method of sterilization: terminal or aseptically filtered

Device information: method of sterilization of syringe, plunger/stopper, needle
For device sterilization, if used for aseptic filling:

What is the method? Radiation (gamma or e-beam ?)
   Parametrically released? Dosimetry?
   Vmax development of max dose (or >25Kgy)?
   Ethylene oxide?

Packaging, primary and possible secondary

How and when are parts assembled?
Drug-device combination- Can it be terminally sterilized? What is the sterilization cycle development?

If moist heat sterilization used,

What is the time and temperature impact on the drug?
What is the time and temperature impact on the device?

Risk assessment is key to product registration and pre-approval inspection by the regulatory agency.
Risk evaluation of each process will influence development of controls.
Are all steps evaluated?

Is ‘assembly’ part of the manufacturing process or performed after the process? (Key risk assessment often missed- assembly of auto/pen injectors)

Is container closure integrity (CCI) performed on filled combination product or with a surrogate?
Is CCI performed during stability?
Device use panel or trial without drug

Actual clinical trial instructions assessment and practice runs
Factors to assess:

- Time of preparation and storage of prepared dose
- Handling of combination product during patient administration
- Specifics of handling if self-administered by patients compared to clinician administering
COLLABORATIVE THINKING IS NOT AN OPTION

Drug developers and Device developers need to communicate what is necessary to protect the patient!

Sharing knowledge is simple, but should be expected more

Using a quality systems approach including experts from both drug and device companies should occur before a combination product is evaluated by the regulators.
THE PATIENT IS OUR ULTIMATE CUSTOMER

Combination products can be robust and safe for patients with adequate collaboration by the drug and device developers with a thorough quality and risk assessment approach.

Our customers depend on us to do it the right way!
Thank You!

Donald Singer
Donald.Singer@Ecolab.com