



PQRI

**Post Approval Changes for Sterile Products
Working Group**

**-Final Report-
April 19, 2007**

TABLE OF CONTENTS

<u>INTRODUCTION</u>	<u>3</u>
<u>WORK GROUP MEMBERS</u>	<u>4</u>
<u>CHANGES NOT COVERED</u>	<u>5</u>
<u>CHANGES COVERED</u>	<u>7</u>
<u>RISK ASSESSMENTS</u>	<u>11</u>
<u>RECOMMENDED REPORTING LEVELS</u>	<u>116</u>
<u>APPENDIX A: PQRI WORK PLAN</u>	<u>117</u>

INTRODUCTION

This report has been developed by the PQRI Post Approval Changes for Sterile Products Working Group formed in September of 2005. The intent of the report, as described in the approved work plan, is to provide regulatory CM&C information that will be of value when considering the development of a Post Approval Guidance for Sterile Drug Products for Human, Veterinary, and Well Characterized Biological Products. Injectable products produced by aseptic processing and terminal sterilization are covered. Drug substance manufacturing is not covered. While this document was not developed for vaccine, allergenic, or blood products, based on the similarities regarding the processes used in manufacturing these sterile products, it should be considered for those areas where applicable. A post approval guidance in this areas is viewed as complementing the Design Space concept as many of the changes discussed in this document will not be covered in the Design Space and will most likely still require some type of filing or notification. The report provides risk assessments for many of the most common types of changes made in the manufacturing process that are currently managed through post approval submissions. The list is not intended to be all inclusive and does not cover changes deemed too complex in nature with too many variables to be evaluated, changes where post approval submissions are not currently required, and changes in finished product specifications and their associated test methods. The work plan is included in its entirety as an appendix.

Based on the risk assessment values developed, recommendations are also provided regarding the level of reporting (using the current FDA regulatory filing categories) that should be considered for each change. All risk assessments have been developed with the assumption that the manufacturing facility where a change is being made is in compliance with cGMPs, with the firm developing, executing, and evaluating all qualifications and validations in compliance with current expectations. Repeatedly during the working group discussions questions arose regarding what changes are and are not managed through the post approval submission process. Therefore, a list of changes where post approval reporting is not required was also generated and is included in the report.

WORKING GROUP MEMBERS

Kristen Anderson, PhD	FDA
Thomas Dolan	Centocor
Patricia Hughes, PhD	FDA
David Hussong, PhD	FDA
Louise Johnson	Vertex
Stephen Liebowitz, PhD	Bristol Myers Squibb
Russell Madsen	The Williamsburg Group
John Metcalfe, PhD	FDA
William Miele, PhD	Pfizer
John Pavlik	Astra Zeneca Pharmaceuticals
Jean Poulos (PQRI MTC Liaison)	Luitpold Pharmaceuticals
Frederic Pratt	Luitpold Pharmaceuticals
Joe Rinella, PhD	Pfizer
Ian Symonds	GSK
Lisa Skeens, PhD	Baxter Healthcare
Brenda Uratani, PhD	FDA
Martin VanTrieste	Amgen
Robyn Wong	Watson Laboratories
Glenn E. Wright (Working Group Chairman)	Eli Lilly
Susan Zordan	Eli Lilly

CHANGES NOT COVERED

As indicated in the introduction the working group did not address the following types of changes.

- Changes where post approval reporting is not currently required.
- Changes that were deemed too complex with too many variables.
- Changes in drug substance and finished product specifications and the associated test methods.

Listed below are the changes discussed and determined to fall within these categories. This should not be considered an all-inclusive list.

Changes where post approval reporting is not required:

- **Facility Related Changes**
 - ❖ Change in gowning practices or materials
 - ❖ Change in utilities
 - Clean steam
 - New system
 - Same type
 - Different type
 - Modification to existing system
 - Change to distribution and storage
 - Change to generation system
 - HVAC
 - Modification to air handlers
 - New air handlers
 - Change of pressures
 - Change in type, size, or location of HEPA filters
 - Change in air velocity
 - Change in air changes (exchange rate)
 - Change in control and monitoring systems
 - Change in humidity and temperature control
 - Change in location of air extraction point(s)
 - Change in location of Grade A/B barrier (i.e. move in Lexan panels)
 - Process gasses
 - Change in source
 - Change in distribution system
 - Change in filtration process (sterile filtration for gases)
- **Equipment Related Changes**
 - ❖ Change in holding/mixing tanks
 - Same design and same operating principle
 - Different design but same operating principle
 - Different operating principle
 - Change in operating parameters
 - ❖ Change in part washers
 - Same design and same operating principle

- Different design but same operating principle
- Different operating principle
- Change in operating parameters
- ❖ Change in tubing or piping (product contact)
 - Material of construction
 - Size (diameter and length)
- ❖ Change in CIP Systems
 - Same design and same operating principle
 - Different design but same operating principle
 - Different operating principle
 - Change in operating parameters
- ❖ Change in environmental monitoring program
 - Sample location
 - Frequency
- **Manufacturing Process Changes**
 - ❖ Changes in cleaning processes
 - Single or multiple products
 - Solvents/detergents
 - Methods
 - Frequency
 - Monitoring
 - Clean and dirty hold times
 - Residual carryover limit

Note: The reader is reminded that while post approval reporting is not required, appropriate change control, qualification, and validation are a clear expectation.

Changes that were deemed too complex with too many variables:

- Change in reprocessing
Resterilization of drug product (terminal sterilization)
- Change in reprocessing
Refiltration of formulated drug product
- Change in container system
(i.e. change between vials, ampoules, syringes, dropper bottles)
- Change in type of gas (overlays)
- Change to allow parametric release for terminally sterilized products.

CHANGES COVERED

Listed below are the changes that were addressed by the working group. A risk assessment for each change was completed and is located in the risk assessment section of this report.

A. Facility Related Changes

A1 Change in site for aseptically processed product

- Same campus/same building/another existing area or line
- Same campus/different building/another existing area or line
- Different site/same company/existing building
- Different site/different company/existing building

A2 Change in site for terminally sterilized product

- Same campus/same building/another existing area or line
- Same campus/different building/another existing area or line
- Different site/same company/existing building
- Different site/different company/existing building

A3 Change in site for aseptically processed product

- Same campus/same building/new or refurbished area or line
- Same campus/different building/new or refurbished area or line
- Different site/same company/new or refurbished area or line
- Different site/different company/new or refurbished area or line

A4 Change in site for terminally sterilized product

- Same campus/same building/new or refurbished area or line
- Same campus/different building/new or refurbished area or line
- Different site/same company/new or refurbished building
- Different site/different company/new or refurbished building

A5 Change in area classification (decrease) in the non-filling area for aseptic processing

where the manufacturing process is open (product exposed) and the product stream does not support microbial growth. (e.g., ISO 7 to ISO 8 or ISO 8 to unclassified)

A6 Change in area classification (decrease) in the non-filling area for aseptic processing

where the manufacturing process is open (product exposed) and the product stream supports microbial growth. (e.g., ISO 7 to ISO 8 or ISO 8 to unclassified)

A7 Change in area classification (decrease) of areas prior to the sterile filtration for

aseptically processed products and prior to sterilization for terminally sterilized products where the manufacturing process is closed (no product exposed). (e.g., ISO 7 to ISO 8 or ISO 8 to unclassified)

A8 Change in facility layout (addition or renovation) in non ISO 5 areas with no change

in classification for aseptically processed product

A9 Change in facility layout (addition or renovation) in non ISO 5 areas with no change

in classification for terminally sterilized product

B. Equipment Related Changes

- [B1](#) Change in washing equipment for elastomer closures
 - Different design and same operating principles
 - Different design and different operating principal
 - Same design and different operating principal

- [B2](#) Change in washing equipment for glass containers (i.e. vials, cartridges, syringe barrels) to be sterilized and depyrogenated via the use of heat
 - Different design and same operating principles
 - Different design and different operating principal
 - Same design and different operating principal

- [B3](#) Change in lyophilizer loading/unloading

- [B4](#) Replacement or addition of a lyophilizer (same performance characteristics)

- [B5](#) Change or addition of a lyophilizer (different performance characteristics)

- [B6](#) Change in dry heat oven operating parameter for aseptically produced product

- [B7](#) Change in dry heat oven operating parameter for terminally sterilized product

- [B8](#) Change or addition of dry heat oven for aseptically produced product

- [B9](#) Change or addition of dry heat oven for terminally sterilized product

- [B10](#) Change in dry heat tunnel operating parameter for aseptically processed product

- [B11](#) Change in dry heat tunnel operating parameter for terminally sterilized product

- [B12](#) Change of dry heat tunnel for aseptically processed product

- [B13](#) Change of dry heat tunnel for terminally sterilized product

- [B14](#) Change in sterile and other filters; Different membrane, different filter, different housing

- [B15](#) Change in sterile and other filters:
 - Change in operating parameters outside validation
 - Change in filter pore size resulting in change in operating parameters

C. Process Related Changes

- [C1](#) Increase in batch size for aseptically filled product

- [C2](#) Increase in batch size for terminally sterilized product

- [C3](#) Change in preparation (washing/siliconization/use of 3rd Party) of elastomeric closures, prior to their sterilization or change to use “ready-to-sterilize” closures (for aseptically processed product)

- [C4](#) Change in preparation (washing/siliconization/use of 3rd Party) of elastomeric closures, prior to their sterilization or change to use “ready-to-sterilize” closures (for terminally sterilized product)

- [C5](#) [Change in filtration duration \(increase\)](#)
- [C6](#) [Change in number of sterilizing filters](#)
- [C7](#) [Change in lyophilization parameters](#)
- [C8](#) [Change in lyophilizer pattern loading](#)
- [C9](#) [Change in sterilization loading pattern for fluid path product contact equipment and components for aseptically processed products](#)
- [C10](#) [Change in sterilization loading pattern for terminally sterilized finished products](#)
- [C11](#) [Change in the method of sterilization \(fluid path product contact equipment, components, and finished product\)](#)
- [C12](#) [Change in sterilization cycle parameters within the existing method \(fluid path product contact equipment, components, and finished product\)](#)
- [C13](#) [Change in compounding mixing speed](#)
- [C14](#) [Changes in the order of addition of ingredients during compounding](#)
- [C15](#) [Change in time limits \(increase\) for pre sterilization hold times for processing steps \(including component preparation\)](#)

D. Component Changes

- [D1](#) [Change of drug substance source \(e.g. different facility or different manufacturer\) for an aseptically produced product](#)
- [D2](#) [Change of drug substance source \(e.g. different facility or different manufacturer\) for terminally sterilized product](#)
- [D3](#) [Change of excipient source \(e.g. different facility or different manufacturer\) for an aseptically produced product](#)
- [D4](#) [Change of excipient source \(e.g. different facility or different manufacturer\) for a terminally sterilized product](#)
- [D5](#) [Change in composition of container materials for solutions, suspensions, emulsions and other dispersed systems for injectables administered intravenously](#)
- [D6](#) [Change in composition of container materials for solutions, suspensions, emulsions and other dispersed systems for injectables administered non-intravenously](#)
- [D7](#) [Change in composition of container materials for powder fill, lyophilized, and other solids for injectables administered intravenously after reconstitution.](#)
- [D8](#) [Change in composition of container materials for powder fill, lyophilized, and other solids for injectables administered non-intravenously after reconstitution.](#)
- [D9](#) [Change in size and/or shape of container for an aseptically produced product](#)

[D10](#) [Change in size and/or shape of container for terminally sterilized sterile product](#)

[D11](#) [Change in composition of closure materials for solutions, suspensions, emulsions and other dispersed systems for injectables administered intravenously](#)

[D12](#) [Change in composition of closure materials for solutions, suspensions, emulsions and other dispersed systems for injectables administered via route other than intravenously](#)

[D13](#) [Change in composition of closure materials for powder fill, lyophilized, and other solids for injectables administered intravenously after reconstitution](#)

[D14](#) [Change in composition of closure materials for powder fill, lyophilized, and other solids for injectables administered via route other than intravenously after reconstitution](#)

[D15](#) [Change of container source, e.g. different facility or different manufacturer](#)

[D16](#) [Change of closure source, e.g. different facility or different manufacturer](#)

E. Changes Where Risk Could Not Be Assessed Because of No Direct Product Quality Impact

[E1](#) [Changes in media fill program](#)

- Change in design (e.g. number filled, duration, interventions, shift changes, number of personnel, etc.)

[E2](#) [Changes in media fill program](#)

- Change in media
- Change in incubation parameters
- Change in methods of media sterilization

[E3](#) [Changes in microbiological test methods for water, EM, raw material, components, identification and In-process bioburden](#)

RISK ASSESSMENTS

The risk assessments were developed using a standard format and process. For each change a set of specific assumptions was made and a listing of possible negative events developed. To evaluate the risk, the Severity, Frequency, and Level of Detectability were evaluated for each negative event using the Risk Assessment Scale below. The type of data needed to support the change was also identified and used when considering the Level of Detectability. As the factors are dependent, the overall risk level is determined by multiplying the factors together. The highest risk level score in this model is 48 and the lowest is 1. The information provided in the "Type of Data Needed to Support the Change" section of each risk assessment should be considered a general evaluation. It is not intended to describe the data to be included in a regulatory submission but rather data that should be generated as part of the change. Listed below is the risk assessment scale used for each change evaluated.

Risk Assessment Scale

This scale and resulting calculation is to be used for assessing the risk of each change:

Value	(S) Severity of Event (Consequence)
1	Negligible: Has no potential to have an adverse effect on the identity, strength, quality, purity or potency of a drug product
2	Minor: Has minimal potential to have an adverse effect on the identity, strength, quality, purity or potency of a drug product
3	Moderate: Has a moderate potential to have an adverse effect on the identity, strength, quality, purity or potency of a drug product
4	Major Has a substantial potential to have an adverse effect on the Identity, strength, quality, purity or potency of a drug product

Value	(F) Frequency Estimation (Likelihood of event occurring)*
1	Highly Unlikely: The probability of the event occurring is so low that it can be assumed that the event will not occur
2	Unlikely: Event not expected to occur, but theoretically possible
3	Likely: Event may occur and/or has occurred in the past
4	Highly Likely: Event expected to occur

***Note: Frequency is not based on the Data Needed to Support the Change.**

Value	(D) Level of Detectability**
1	Readily Detectable: Will be detected
2	May Be Detectable: May be detected
3	Not Detectable: No mechanism for detection

****Note: Detectability is based on In-Process, Release Testing and Data Needed to Support the Change.**

The Level of Risk is calculated as:

$$\text{Risk} = (\text{S}) \times (\text{F}) \times (\text{D})$$

A set of overall assumptions has been made for all of the risk assessments generated. These are:

- Equipment is properly qualified and validated.
- Manufacturing facility where the change is being made is in compliance with cGMPs.
- All qualifications and validations related to the change are developed, executed, and evaluated in compliance with current expectations.
- The data set identified in the “Type of Data Needed to Support the Change” section of each assessment has been generated.

Several conclusions were reached about specific types of data and their ability to detect specific negative events in evaluating the “Level of Detectability”. Similarly, for the “Severity of Event” a set of standard conclusions was reached regarding the rating of specific events. The tables below list these conclusions.

LEVEL OF DETECTABILITY

Negative Event	Data to Detect Event	Level of Detectability	Rationale
Production of non sterile drug product	Media fill data	May Be Detectable: (2)	Media fill can not duplicate all possible conditions
Production of non sterile drug product	Sterility test data	Not Detectable: (3)	Sample size is so small that statistically the ability to detect low levels of contamination is extremely limited.

SEVERITY OF EVENTS

Negative Event	Severity of Event
Product containing elevated levels of endotoxins (pyrogens)*	Major: Has a substantial potential to have an adverse effect on the identity, strength, quality, purity or potency of a drug product (4)
Degradation of product	Moderate: Has a moderate potential to have an adverse effect on the identity, strength, quality, purity or potency of a drug product (3)

*Note: The term endotoxins is used in the evaluations rather than the term pyrogens. The level of endotoxin present in a pharmaceutical product is an accepted indicator of its pyrogenicity.

Risk Assessment #A1

Change Description in Detail:

- Change in site for aseptically processed product
- Same campus/same building/another existing area or line
 - Same campus/different building/another existing area or line
 - Different site/same company/existing building
 - Different site/different company/existing building

Assumptions and Comments:

- Area has been approved for manufacturing similar products
- No process changes, including component preparation
- Same type of equipment (same design and operating principles)

Possible Events:

(Negative events that could occur as a result of the change)

- A. Product manufactured in new area or line does not meet established physical and chemical release acceptance criteria or test results are not within ranges of historical lots from before the change (e.g., potency, related substances, non viable particulates, endotoxins)

- B. Decreased level of sterility assurance resulting in production of a non-sterile product

Severity of Event (S):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

- A. **Major:** Has a substantial potential to have an adverse effect on the identity, strength, quality, purity or potency of a drug product **(4)**

- B. **Major:** Has a substantial potential to have an adverse effect on the identity, strength, quality, purity or potency of a drug product **(4)**

Frequency Estimation (F):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

- A. **Unlikely:** Event not expected to occur, but theoretically possible **(2)**

- B. **Likely:** Event may occur and/or has occurred in the past **(3)**

Level of Detectability (D):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

- A. **Readily Detectable:** Will be detected **(1)**

- B. **May Be Detectable:** May be detected **(2)**

Type of Data Needed to Support the Change:

- A.
- Comparison of batch release data from lots manufactured prior to change and after change
 - Product process validation in new area
 - Cleaning validation
 - Stability data

- B. - Media fills if not within the parameters of other products manufactured in new area or line
- Component sterilization if applicable

Risk Level of Change Based on Assessment:

Event A

$$\begin{array}{c} \boxed{4} \\ (S) \end{array} \times \begin{array}{c} \boxed{2} \\ (F) \end{array} \times \begin{array}{c} \boxed{1} \\ (D) \end{array} = \begin{array}{c} \boxed{8} \\ \text{Risk Level} \end{array}$$

Event B

$$\begin{array}{c} \boxed{4} \\ (S) \end{array} \times \begin{array}{c} \boxed{3} \\ (F) \end{array} \times \begin{array}{c} \boxed{2} \\ (D) \end{array} = \begin{array}{c} \boxed{24} \\ \text{Risk Level} \end{array}$$

Overall Risk Level:

$$\boxed{24}$$

Risk Assessment #A2

Change Description in Detail:

- Change in site for terminally sterilized product
- Same campus/same building/another existing area or line
 - Same campus/different building/another existing area or line
 - Different site/same company/existing building
 - Different site/different company/existing building

Assumptions and Comments:

- Area has been approved for manufacturing similar products
- No process changes, including component preparation
- Same type of equipment (same design and operating principles)
- Terminal sterilization process has not changed

Possible Events:

(Negative events that could occur as a result of the change)

A. Product manufactured in new area or line does not meet established physical and chemical release acceptance criteria or test results are not within ranges of historical lots from before the change (e.g., potency, related substances, non viable particulates or endotoxins)

B. Decreased level of sterility assurance resulting in production of a non-sterile product

Severity of Event (S):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

A. **Major:** Has a substantial potential to have an adverse effect on the identity, strength, quality, purity or potency of a drug product **(4)**

B. **Major:** Has a substantial potential to have an adverse effect on the identity, strength, quality, purity or potency of a drug product **(4)**

Frequency Estimation (F):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

A. **Unlikely:** Event not expected to occur, but theoretically possible **(2)**

B. **Highly Unlikely:** The probability of the event occurring is so low that it can be assumed that the event will not occur **(1)**

Level of Detectability (D):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

A. **Readily Detectable:** Will be detected **(1)**

B. **Readily Detectable:** Will be detected **(1)**

Type of Data Needed to Support the Change:

- A. - Comparison of batch release data from lots manufactured prior to change and after change
- Product process validation in new area

- Cleaning validation
- Stability data

B. - Terminal sterilization cycle validation

Risk Level of Change Based on Assessment:

Event A

$$\begin{array}{c} \boxed{4} \\ (S) \end{array} \times \begin{array}{c} \boxed{2} \\ (F) \end{array} \times \begin{array}{c} \boxed{1} \\ (D) \end{array} = \begin{array}{c} \boxed{8} \\ \text{Risk Level} \end{array}$$

Event B

$$\begin{array}{c} \boxed{4} \\ (S) \end{array} \times \begin{array}{c} \boxed{1} \\ (F) \end{array} \times \begin{array}{c} \boxed{1} \\ (D) \end{array} = \begin{array}{c} \boxed{4} \\ \text{Risk Level} \end{array}$$

Overall Risk Level:

$\boxed{8}$

Risk Assessment #A3

Change Description in Detail:

Change in site for aseptically processed product

- Same campus/same building/new or refurbished area or line
- Same campus/different building/new or refurbished area or line
- Different site/same company/new or refurbished area or line
- Different site/different company/new or refurbished area or line)

Change in facility layout (renovation or addition) in the ISO 5 and or immediate adjacent areas for aseptically processed product

Assumptions and Comments:

- Changes impact aseptic block area
- No process changes, including component preparation
- Same type of equipment (same design and operating principles)
- Renovation or addition brings equivalent (meets current standards) or improved engineering technologies and improved material, personnel and product flows

Possible Events:

(Negative events that could occur as a result of the change)

A. Product manufactured in new or refurbished area does not meet established physical and chemical release acceptance criteria or test results are not within ranges of historical lots from before the change (e.g. potency, related substances, non-viable particulates or endotoxins)

B. Decreased level of sterility assurance resulting in production of a non-sterile product

C. Increased variability of filling resulting in product with inaccurate fill/dose

Severity of Event (S):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

A. **Major:** Has a substantial potential to have an adverse effect on the identity, strength, quality, purity or potency of a drug product **(4)**

B. **Major:** Has a substantial potential to have an adverse effect on the identity, strength, quality, purity or potency of a drug product **(4)**

C. **Major:** Has a substantial potential to have an adverse effect on the identity, strength, quality, purity or potency of a drug product **(4)**

Frequency Estimation (F):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

A. **Unlikely:** Event not expected to occur, but theoretically possible **(2)**

B. **Likely:** Event may occur and/or has occurred in the past **(3)**

C. **Unlikely:** Event not expected to occur, but theoretically possible **(2)**

Level of Detectability (D):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

A. **Readily Detectable:** Will be detected (1)

B. **May be Detectable:** May be detected (2)

C. **Readily Detectable:** Will be detected (1)

Type of Data Needed to Support the Change:

A. - Comparison of batch release data from lots manufactured prior to change and after change
- Product process validation in new area or in refurbished area if applicable
- Cleaning validation
- Stability data

B. - Media fills
- Environmental monitoring qualification
- Component sterilization if applicable
- Air flow pattern testing

C. - Product process validation in new area or in refurbished area if applicable

Risk Level of Change Based on Assessment:

Event A
$$\begin{array}{c} \boxed{4} \\ (S) \end{array} \times \begin{array}{c} \boxed{2} \\ (F) \end{array} \times \begin{array}{c} \boxed{1} \\ (D) \end{array} = \begin{array}{c} \boxed{8} \\ \text{Risk Level} \end{array}$$

Event B
$$\begin{array}{c} \boxed{4} \\ (S) \end{array} \times \begin{array}{c} \boxed{3} \\ (F) \end{array} \times \begin{array}{c} \boxed{2} \\ (D) \end{array} = \begin{array}{c} \boxed{24} \\ \text{Risk Level} \end{array}$$

Event C
$$\begin{array}{c} \boxed{4} \\ (S) \end{array} \times \begin{array}{c} \boxed{2} \\ (F) \end{array} \times \begin{array}{c} \boxed{1} \\ (D) \end{array} = \begin{array}{c} \boxed{8} \\ \text{Risk Level} \end{array}$$

Overall Risk Level:

$\boxed{24}$

Risk Assessment #A4

Change Description in Detail:

Change in site for terminally sterilized product

- Same campus/same building/new or refurbished area or line
- Same campus/different building/new or refurbished area or line
- Different site/same company/new or refurbished building
- Different site/different company/new or refurbished building

Change in facility layout (renovation or addition) in the ISO 5 and or immediate adjacent areas for terminally sterilized product

Assumptions and Comments:

- No process changes, including component preparation
- Terminal sterilization process not changed
- Same type of equipment (same design and operating principles)
- Renovation or addition brings equivalent (meets current standards) or improved engineering technologies and improved material, personnel and product flows

Possible Events:

(Negative events that could occur as a result of the change)

A. Product manufactured in new or refurbished area does not meet established physical and chemical release acceptance criteria or test results are not within ranges of historical lots from before the change (e.g. potency, related substances, non-viable particulates or endotoxins)

B. Decreased level of sterility assurance resulting in production of a non-sterile product

Severity of Event (S):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

A. **Major:** Has a substantial potential to have an adverse effect on the identity, strength, quality, purity or potency of a drug product **(4)**

B. **Major:** Has a substantial potential to have an adverse effect on the identity, strength, quality, purity or potency of a drug product **(4)**

Frequency Estimation (F):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

A. **Unlikely:** Event not expected to occur, but theoretically possible **(2)**

B. **Highly Unlikely:** The probability of the event occurring is so low that it can be assumed that the event will not occur **(1)**

Level of Detectability (D):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

A. **Readily Detectable:** Will be detected **(1)**

B. **Readily Detectable:** Will be detected **(1)**

Type of Data Needed to Support the Change:

- A. - Comparison of batch release data from lots manufactured prior to change and after change
- Product process validation in new area or refurbished area if applicable
- Cleaning validation
- Stability data

- B. - Environmental qualification
- Terminal sterilization cycle validation

Risk Level of Change Based on Assessment:

Event A

$$\frac{4}{(S)} \times \frac{2}{(F)} \times \frac{1}{(D)} = \frac{8}{\text{Risk Level}}$$

Event B

$$\frac{4}{(S)} \times \frac{1}{(F)} \times \frac{1}{(D)} = \frac{4}{\text{Risk Level}}$$

Overall Risk Level:

$$\frac{8}{\text{Risk Level}}$$

Risk Assessment #A5

Change Description in Detail:

Change in area classification (decrease in class/grade) in the non-filling area for aseptic processing where the manufacturing process is open (product exposed) and the product stream does not support microbial growth. (e.g., ISO 7 to ISO 8 or ISO 8 to unclassified)

Assumptions and Comments:

- No process changes, including hold times
- No equipment changes
- Established in-process limits for microbial control are in place
- The change occurs in processing areas used for manufacturing steps prior to sterile filtration

Possible Events:

(Negative events that could occur as a result of the change)

A. Bioburden increases in the product prior to the filtration step exceeding the retentive capabilities of the sterilizing filter and resulting in non sterile product

B. Bioburden increases in the product prior to sterilization causing an increase in endotoxin levels in the product

Severity of Event (S):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

A. **Major:** Has a substantial potential to have an adverse effect on the identity, strength, quality, purity or potency of a drug product **(4)**

B. **Major:** Has a substantial potential to have an adverse effect on the identity, strength, quality, purity or potency of a drug product **(4)**

Frequency Estimation (F):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

A. **Highly Unlikely:** The probability of the event occurring is so low that it can be assumed that the event will not occur **(1)**

B. **Highly Unlikely:** The probability of the event occurring is so low that it can be assumed that the event will not occur **(1)**

Level of Detectability (D):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

A. **Readily Detectable:** Will be detected **(1)**

B. **Readily Detectable:** Will be detected **(1)**

Type of Data Needed to Support the Change:

- A. - Environmental qualification of the area for the new level
- Evidence that process intermediates do not support microbial growth
- Validation of process hold times under the new conditions (bioburden and endotoxin)

- Comparability of release data of lots manufactured before and after change

- B. - Environmental qualification of the area for the new level
- Evidence that process intermediates do not support microbial growth
- Validation of process hold times under the new conditions (bioburden and endotoxin)
- Comparability of release data of lots manufactured before and after change

Risk Level of Change Based on Assessment:

Event A

$$\frac{4}{(S)} \times \frac{1}{(F)} \times \frac{1}{(D)} = \frac{4}{\text{Risk Level}}$$

Event B

$$\frac{4}{(S)} \times \frac{1}{(F)} \times \frac{1}{(D)} = \frac{4}{\text{Risk Level}}$$

Overall Risk Level:

4

Risk Assessment #A6

Change Description in Detail:

Change in area classification (decrease) in the non-filling area for aseptic processing where the manufacturing process is open (product exposed) and the product stream supports microbial growth (e.g. ISO 7 to ISO 8 or ISO 8 to unclassified)

Assumptions and Comments:

- No process changes, including hold times
- No equipment changes
- Established in-process limits for microbial control are in place
- The change occurs in processing areas used for manufacturing steps prior to sterile filtration

Possible Events:

(Negative events that could occur as a result of the change)

A. Bioburden increases in the product prior to the filtration step exceeding the retentive capabilities of the sterilizing filter and resulting in non sterile product

B. Bioburden increases in the product prior to sterilization causing an increase in endotoxin levels in the product.

Severity of Event (S):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

A. **Major:** Has a substantial potential to have an adverse effect on the identity, strength, quality, purity or potency of a drug product **(4)**

B. **Major:** Has a substantial potential to have an adverse effect on the identity, strength, quality, purity or potency of a drug product **(4)**

Frequency Estimation (F):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

A. **Likely:** Event may occur and / or has occurred in the past **(3)**

B. **Likely:** Event may occur and / or has occurred in the past **(3)**

Level of Detectability (D):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

A. **Ready Detectable:** Will be detected **(1)**

B. **Ready Detectable:** Will be detected **(1)**

Type of Data Needed to Support the Change:

- A. - Environmental qualification of the area for the new level
- Validation of process hold times under the new conditions (bioburden and endotoxin)
- Comparability of release data of lots manufactured before and after change

- Environmental qualification of the area for the new level
- Validation of process hold times under the new conditions (bioburden and endotoxin)
- Comparability of release data of lots manufactured before and after change

Risk Level of Change Based on Assessment:

Event A

$$\begin{array}{c} \boxed{4} \\ (S) \end{array} \times \begin{array}{c} \boxed{3} \\ (F) \end{array} \times \begin{array}{c} \boxed{1} \\ (D) \end{array} = \begin{array}{c} \boxed{12} \\ \text{Risk Level} \end{array}$$

Event B

$$\begin{array}{c} \boxed{4} \\ (S) \end{array} \times \begin{array}{c} \boxed{3} \\ (F) \end{array} \times \begin{array}{c} \boxed{1} \\ (D) \end{array} = \begin{array}{c} \boxed{12} \\ \text{Risk Level} \end{array}$$

Overall Risk Level:

$$\boxed{12}$$

Risk Assessment #A7

Change Description in Detail:

Change in area classification (decrease) of areas prior to the sterile filtration for aseptically processed products and prior to sterilization for terminally sterilized products where the manufacturing process is closed (no product exposed) (e.g. ISO 7 to ISO 8 or ISO 8 to unclassified)

Assumptions and Comments:

- No process changes, including hold times
- No equipment changes
- Established in-process limits for microbial control are in place
- Applies to both aseptically processed products before the sterile filtration step and terminally sterilized products before sterilization
- Integrity of the closed system has been demonstrated (no product exposed to environment)

Possible Events:

(Negative events that could occur as a result of the change)

A. Bioburden increases in the product prior to the filtration step exceeding the retentive capabilities of the sterilizing filter or prior to terminal sterilization causing the sterilization cycle to be ineffective resulting in non-sterile product

B. Bioburden increases in the product prior to sterilization causing an increase in endotoxin levels in the product

Severity of Event (S):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

A. **Major:** Has a substantial potential to have an adverse effect on the identity, strength, quality, purity or potency of a drug product **(4)**

B. **Major:** Has a substantial potential to have an adverse effect on the identity, strength, quality, purity or potency of a drug product **(4)**

Frequency Estimation (F):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

A. **Highly Unlikely:** The probability of the event is so low that it can be assumed that the event will not occur **(1)**

B. **Highly Unlikely:** The probability of the event is so low that it can be assumed that the event will not occur **(1)**

Level of Detectability (D):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

A. **Readily Detectable:** Will be detected **(1)**

B. **Readily Detectable:** Will be detected **(1)**

Type of Data Needed to Support the Change:

A. - Environmental qualification of the area for the new level

B. - Environmental qualification of the area for the new level

Risk Level of Change Based on Assessment:

Event A

$$\begin{array}{c} \boxed{4} \\ (S) \end{array} \times \begin{array}{c} \boxed{1} \\ (F) \end{array} \times \begin{array}{c} \boxed{1} \\ (D) \end{array} = \begin{array}{c} \boxed{4} \\ \text{Risk Level} \end{array}$$

Event B

$$\begin{array}{c} \boxed{4} \\ (S) \end{array} \times \begin{array}{c} \boxed{1} \\ (F) \end{array} \times \begin{array}{c} \boxed{1} \\ (D) \end{array} = \begin{array}{c} \boxed{4} \\ \text{Risk Level} \end{array}$$

Overall Risk Level:

$\boxed{4}$

Risk Assessment #A8

Change Description in Detail:

Change in facility layout (addition or renovation) in non ISO 5 areas with no change in classification for aseptically processed product

Assumptions and Comments:

- Area has been approved for manufacturing similar products
- No process changes, including component preparation
- Same type of equipment (same design and operating principles)
- Areas are not immediately adjacent to the ISO 5 area
- Addition or renovation brings equivalent (meets current standards) or improved engineering technologies and improved material, personnel and product flows

Possible Events:

(Negative events that could occur as a result of the change)

A. Product manufactured in new area or line does not meet established physical and chemical release acceptance criteria or test results are not within ranges of historical lots from before the change (e.g., potency, related substances, non-viable particulates, or endotoxins)

B. Decreased level of sterility assurance resulting in production of a non-sterile product

Severity of Event (S):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

A. **Major:** Has a substantial potential to have an adverse effect on the identity, strength, quality, purity or potency of a drug product **(4)**

B. **Major:** Has a substantial potential to have an adverse effect on the identity, strength, quality, purity or potency of a drug product **(4)**

Frequency Estimation (F):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

A. **Unlikely:** Event not expected to occur, but theoretically possible **(2)**

B. **Unlikely:** Event not expected to occur, but theoretically possible **(2)**

Level of Detectability (D):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

A. **Readily Detectable:** Will be detected **(1)**

B. **May be Detectable:** May be detected **(2)**

Type of Data Needed to Support the Change:

- A.
- Comparison of batch release data from lots manufactured prior to change and after change
 - Product process validation (if applicable)
 - Stability data

- B. - Media fills
- Component sterilization if applicable

Risk Level of Change Based on Assessment:

Event A

$$\begin{array}{c} \boxed{4} \\ \text{(S)} \end{array} \times \begin{array}{c} \boxed{2} \\ \text{(F)} \end{array} \times \begin{array}{c} \boxed{1} \\ \text{(D)} \end{array} = \begin{array}{c} \boxed{8} \\ \text{Risk Level} \end{array}$$

Event B

$$\begin{array}{c} \boxed{4} \\ \text{(S)} \end{array} \times \begin{array}{c} \boxed{2} \\ \text{(F)} \end{array} \times \begin{array}{c} \boxed{2} \\ \text{(D)} \end{array} = \begin{array}{c} \boxed{16} \\ \text{Risk Level} \end{array}$$

Overall Risk Level:

$$\boxed{16}$$

Risk Assessment #A9

Change Description in Detail:

Change in facility layout (addition or renovation) in non ISO 5 areas with no change in classification for terminally sterilized product

Assumptions and Comments:

- Area has been approved for manufacturing similar products
- No process changes, including component preparation
- Same type of equipment (same design and operating principles)
- Areas are not immediately adjacent to the ISO 5 area
- Addition or renovation brings equivalent (meets current standards) or improved engineering technologies and improved material, personnel and product flows

Possible Events:

(Negative events that could occur as a result of the change)

A. Product manufactured in new area or line does not meet established physical and chemical release acceptance criteria or test results are not within ranges of historical lots from before the change (e.g. potency, related substances, non-viable particulates or endotoxins)

B. Decreased level of sterility assurance resulting in production of a non-sterile product

Severity of Event (S):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

A. **Major:** Has a substantial potential to have an adverse effect on the identity, strength, quality, purity or potency of a drug product **(4)**

B. **Major:** Has a substantial potential to have an adverse effect on the identity, strength, quality, purity or potency of a drug product **(4)**

Frequency Estimation (F):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

A. **Unlikely:** Event not expected to occur, but theoretically possible **(2)**

B. **Highly Unlikely:** The probability of the event occurring is so low that it can be assumed that the event will not occur **(1)**

Level of Detectability (D):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

A. **Readily Detectable:** Will be detected **(1)**

B. **Readily Detectable:** Will be detected **(1)**

Type of Data Needed to Support the Change:

- A. - Comparison of batch release data from lots manufactured prior to change and after change
- Product process validation (if applicable)
- Stability data

- B. - Terminal sterilization cycle validation (if applicable)

Risk Level of Change Based on Assessment:

Event A

$$\begin{array}{c} \boxed{4} \\ (S) \end{array} \times \begin{array}{c} \boxed{2} \\ (F) \end{array} \times \begin{array}{c} \boxed{1} \\ (D) \end{array} = \begin{array}{c} \boxed{8} \\ \text{Risk Level} \end{array}$$

Event B

$$\begin{array}{c} \boxed{4} \\ (S) \end{array} \times \begin{array}{c} \boxed{1} \\ (F) \end{array} \times \begin{array}{c} \boxed{1} \\ (D) \end{array} = \begin{array}{c} \boxed{4} \\ \text{Risk Level} \end{array}$$

Overall Risk Level:

$$\boxed{8}$$

Risk Assessments #B1

Change Description in Detail:

Change in washing equipment for elastomer closures - Different design and same operating principles - Different design and different operating principles - Same design and different operating principles

Assumptions and Comments:

- None

Possible Events:

(Negative events that could occur as a result of the change)

A. Closures washed with new equipment of different design, different operating parameters, or both have a high level of endotoxins present causing the final product to be contaminated with endotoxins

B. Closures washed with new equipment of different design, different operating parameters, or both have residual detergent present causing the final product to be contaminated with detergent
--

C. Closures washed with new equipment of different design, different operating parameters, or both have a high particulate load causing the final product to be contaminated with particulates
--

Severity of Event (S):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

A. Major: Has a substantial potential to have an adverse effect on the identity, strength, quality, purity or potency of a drug product (4)

B. Major: Has a substantial potential to have an adverse effect on the identity, strength, quality, purity or potency of a drug product (4)

C. Moderate: Has a moderate potential to have an adverse effect on the identity, strength, quality, purity or potency of a drug product (3)

Frequency Estimation (F):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

A. Unlikely: Event not expected to occur, but theoretically possible (2)
--

B. Unlikely: Event not expected to occur, but theoretically possible (2)
--

C. Unlikely: Event not expected to occur, but theoretically possible (2)
--

Level of Detectability (D):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

A. Readily Detectable: Will be detected (1)

B. Readily Detectable: Will be detected (1)

C. **Readily Detectable:** Will be detected (1)

Type of Data Typically Needed to Support the Change:

A. - Cleaning validation (endotoxin reduction testing, cleaning agent residue testing, particulate load testing)

B. - Cleaning validation (endotoxin reduction testing, cleaning agent residue testing, particulate load testing)

C. - Cleaning validation (endotoxin reduction testing, cleaning agent residue testing, particulate load testing)

Risk Level of Change Based on Assessment:

Event A

$$\begin{array}{c} \boxed{4} \\ (S) \end{array} \times \begin{array}{c} \boxed{2} \\ (F) \end{array} \times \begin{array}{c} \boxed{1} \\ (D) \end{array} = \begin{array}{c} \boxed{8} \\ \text{Risk Level} \end{array}$$

Event B

$$\begin{array}{c} \boxed{4} \\ (S) \end{array} \times \begin{array}{c} \boxed{2} \\ (F) \end{array} \times \begin{array}{c} \boxed{1} \\ (D) \end{array} = \begin{array}{c} \boxed{8} \\ \text{Risk Level} \end{array}$$

Event C

$$\begin{array}{c} \boxed{3} \\ (S) \end{array} \times \begin{array}{c} \boxed{2} \\ (F) \end{array} \times \begin{array}{c} \boxed{1} \\ (D) \end{array} = \begin{array}{c} \boxed{6} \\ \text{Risk Level} \end{array}$$

Overall Risk Level:

$$\boxed{8}$$

Risk Assessment #B2

Change Description in Detail:

Change in washing equipment for glass containers (i.e. vials, cartridges, syringe barrels) to be sterilized and depyrogenated via the use of heat

- Different design and same operating principles
- Different design and different operating principles
- Same design and different operating principles

Assumptions and Comments:

- None

Possible Events:

(Negative events that could occur as a result of the change)

A. Containers washed with new equipment of different design, different operating parameters, or both are contaminated with residual materials introduced during the manufacture, storage or shipping of the containers resulting in contaminated product

B. Containers washed with new equipment of different design, different operating parameters, or both have a high particulate load causing the final product to be contaminated with particulates

Severity of Event (S):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

A. **Major:** Has a substantial potential to have an adverse effect on the identity, strength, quality, purity or potency of a drug product **(4)**

B. **Moderate:** Has a moderate potential to have an adverse effect on the identity, strength, quality, purity or potency of a drug product **(3)**

Frequency Estimation (F):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

A. **Unlikely:** Event not expected to occur, but theoretically possible **(2)**

B. **Unlikely:** Event not expected to occur, but theoretically possible **(2)**

Level of Detectability (D):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

A. **Readily Detectable:** Will be detected **(1)**

B. **Readily Detectable:** Will be detected **(1)**

Type of Data Typically Needed to Support the Change:

A. - Cleaning validation studies based on the process used (i.e. spray coverage testing, particulate load testing, detergent residue testing)

B. - Cleaning validation studies based on the process used (i.e. spray coverage testing, particulate load testing, detergent residue testing)

Risk Level of Change Based on Assessment:

Event A

$$\begin{array}{c} \boxed{4} \\ (S) \end{array} \times \begin{array}{c} \boxed{2} \\ (F) \end{array} \times \begin{array}{c} \boxed{1} \\ (D) \end{array} = \begin{array}{c} \boxed{8} \\ \text{Risk Level} \end{array}$$

Event B

$$\begin{array}{c} \boxed{3} \\ (S) \end{array} \times \begin{array}{c} \boxed{2} \\ (F) \end{array} \times \begin{array}{c} \boxed{1} \\ (D) \end{array} = \begin{array}{c} \boxed{6} \\ \text{Risk Level} \end{array}$$

Overall Risk Level:

$$\boxed{8}$$

Risk Assessment #B3

Change Description in Detail:

Change in lyophilizer loading/unloading (e.g. manual to automated)

Assumptions and Comments:

No change in lyophilizer equipment

Possible Events:

(Negative events that could occur as a result of the change)

A. Change in loading/unloading results in a reduction of aseptic conditions leading to non-sterile product

Severity of Event (S):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

A. **Major:** Has a substantial potential to have an adverse effect on the identity, strength, quality, purity or potency of a drug product **(4)**

Frequency Estimation (F):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

A. **Likely:** Event may occur and/or has occurred in the past **(3)**

Level of Detectability (D):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

A. **May Be Detectable:** May be detected **(2)**

Type of Data Needed to Support the Change:

A. - Air pattern testing
- Media fills

Risk Level of Change Based on Assessment:

Event A

$$\begin{array}{c} \boxed{4} \\ (S) \end{array} \times \begin{array}{c} \boxed{3} \\ (F) \end{array} \times \begin{array}{c} \boxed{2} \\ (D) \end{array} = \begin{array}{c} \boxed{24} \\ \text{Risk Level} \end{array}$$

Overall Risk Level:

24

Risk Assessment #B4

Change Description in Detail:

Replacement or addition of a lyophilizer (same performance characteristics)

Assumptions and Comments:

- Relates to a facility in which lyophilizers are already present
- Same performance characteristics (shelf temperature mapping, automation control strategy, qualification parameters)
- No change in lyophilization cycle

Possible Events:

(Negative events that could occur as a result of the change)

A. Change in lyophilized plug qualities (moisture, color, appearance, etc) that lead to reduced product potency or increased related substances over shelf life

B. Change in the lyophilizer's physical design (shape or function located in the aseptic area) results in changes in air flow patterns causing a reduction of the aseptic conditions during loading/unloading of vials leading to non-sterile product

C. Sterilization of lyophilizer not effective resulting in non-sterile product

D. Cleaning of lyophilizer not effective resulting in contaminated product

Severity of Event (S):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

A. **Major:** Has a substantial potential to have an adverse effect on the identity, strength, quality, purity or potency of a drug product. **(4)**

B. **Major:** Has a substantial potential to have an adverse effect on the identity, strength, quality, purity or potency of a drug product **(4)**

C. **Major:** Has a substantial potential to have an adverse effect on the identity, strength, quality, purity or potency of a drug product **(4)**

D. **Major:** Has a substantial potential to have an adverse effect on the identity, strength, quality, purity or potency of a drug product **(4)**

Frequency Estimation (F):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

A. **Unlikely:** Event not expected to occur, but theoretically possible **(2)**

B. **Likely:** Event may occur and/or has occurred in the past **(3)**

C. **Unlikely:** Event not expected to occur, but theoretically possible **(2)**

D. **Highly Unlikely:** The probability of the event occurring is so low that it can be assumed that the event will not occur **(1)**

Note: A "Highly Unlikely" rating was assigned because any contamination present in the lyophilizer would most likely be located on non-contact product surfaces.

Level of Detectability (D):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

A. **Readily Detectable:** Will be detected **(1)**

B. **May Be Detectable:** May be detected **(2)**

C. **Readily Detectable:** Will be detected **(1)**

D. **Readily Detectable:** Will be detected **(1)**

Type of Data Needed to Support the Change:

A. - Verification of comparability between new lyophilizer and existing lyophilizer (shelf temperature mapping, automation control strategy, qualification parameters)
- Expanded product testing for first lot at worst case locations (validation level sampling)
- First lot placed on stability

B. - Air pattern testing (smoke test)
- Media fills

C. - Lyophilizer sterilization validation

D. - Lyophilizer cleaning validation

Risk Level of Change Based on Assessment:

Event A

$$\begin{array}{c} \boxed{4} \\ (S) \end{array} \times \begin{array}{c} \boxed{2} \\ (F) \end{array} \times \begin{array}{c} \boxed{1} \\ (D) \end{array} = \begin{array}{c} \boxed{8} \\ \text{Risk Level} \end{array}$$

Event B

$$\begin{array}{c} \boxed{4} \\ (S) \end{array} \times \begin{array}{c} \boxed{3} \\ (F) \end{array} \times \begin{array}{c} \boxed{2} \\ (D) \end{array} = \begin{array}{c} \boxed{24} \\ \text{Risk Level} \end{array}$$

Event C

$$\begin{array}{c} \boxed{4} \\ (S) \end{array} \times \begin{array}{c} \boxed{2} \\ (F) \end{array} \times \begin{array}{c} \boxed{1} \\ (D) \end{array} = \begin{array}{c} \boxed{8} \\ \text{Risk Level} \end{array}$$

Event D

$$\begin{array}{c} \boxed{4} \\ (S) \end{array} \times \begin{array}{c} \boxed{1} \\ (F) \end{array} \times \begin{array}{c} \boxed{1} \\ (D) \end{array} = \begin{array}{c} \boxed{4} \\ \text{Risk Level} \end{array}$$

Overall Risk Level:

24

Risk Assessment #B5

Change Description in Detail:

Change or addition of a lyophilizer (different performance characteristics)

Assumptions and Comments:

- Relates to a facility in which lyophilizers are already present
- No change in lyophilization cycle

Possible Events:

(Negative events that could occur as a result of the change)

A. Change in lyophilized plug qualities (moisture, color, appearance, etc) that lead to reduced product potency or increased related substances over shelf life

B. Change in the lyophilizer's physical design (shape or function located in the aseptic area) results in changes in air flow patterns causing a reduction of the aseptic conditions during loading/unloading of vials leading to non-sterile product

C. Sterilization of lyophilizer not effective resulting in non-sterile product

D. Cleaning of lyophilizer not effective resulting in contaminated product

Severity of Event (S):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

A. **Major:** Has a substantial potential to have an adverse effect on the identity, strength, quality, purity or potency of a drug product **(4)**

B. **Major:** Has a substantial potential to have an adverse effect on the identity, strength, quality, purity or potency of a drug product **(4)**

C. **Major:** Has a substantial potential to have an adverse effect on the identity, strength, quality, purity or potency of a drug product **(4)**

D. **Major:** Has a substantial potential to have an adverse effect on the identity, strength, quality, purity or potency of a drug product **(4)**

Frequency Estimation (F):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

A. **Likely:** Event may occur and/or has occurred in the past **(3)**

B. **Likely:** Event may occur and/or has occurred in the past **(3)**

C. **Unlikely:** Event not expected to occur, but theoretically possible **(2)**

D. **Highly Unlikely:** The probability of the event occurring is so low that it can be assumed that the event will not occur **(1)***

* Note: A "Highly Unlikely" rating was assigned because any contamination present in the lyophilizer would most likely be located on non-contact product surfaces

Level of Detectability (D):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

A. **Readily Detectable:** Will be detected **(1)**

B. **May Be Detectable:** May be detected **(2)**

C. **Readily Detectable:** Will be detected **(1)**

D. **Readily Detectable:** Will be detected **(1)**

Type of Data Needed to Support the Change:

A.
- Lyophilization process validation
- Stability data

B. - Air pattern testing (smoke test)
- Media fills

C. - Lyophilizer sterilization validation

D. - Lyophilizer cleaning validation

Risk Level of Change Based on Assessment:

Event A

$$\begin{array}{c} \boxed{4} \\ (S) \end{array} \times \begin{array}{c} \boxed{3} \\ (F) \end{array} \times \begin{array}{c} \boxed{1} \\ (D) \end{array} = \begin{array}{c} \boxed{12} \\ \text{Risk Level} \end{array}$$

Event B

$$\begin{array}{c} \boxed{4} \\ (S) \end{array} \times \begin{array}{c} \boxed{3} \\ (F) \end{array} \times \begin{array}{c} \boxed{2} \\ (D) \end{array} = \begin{array}{c} \boxed{24} \\ \text{Risk Level} \end{array}$$

Event C

$$\begin{array}{c} \boxed{4} \\ (S) \end{array} \times \begin{array}{c} \boxed{2} \\ (F) \end{array} \times \begin{array}{c} \boxed{1} \\ (D) \end{array} = \begin{array}{c} \boxed{8} \\ \text{Risk Level} \end{array}$$

Event D

$$\begin{array}{c} \boxed{4} \\ (S) \end{array} \times \begin{array}{c} \boxed{1} \\ (F) \end{array} \times \begin{array}{c} \boxed{1} \\ (D) \end{array} = \begin{array}{c} \boxed{4} \\ \text{Risk Level} \end{array}$$

Overall Risk Level:

$\boxed{24}$

Risk Assessment #B6

Change Description in Detail:

Change in dry heat oven operating parameter for aseptically produced product

Assumptions and Comments:

- Oven is used for depyrogenation and sterilization of glass product containers
- Containers being sterilized and depyrogenated are in covered trays or pans

Possible Events:

(Negative events that could occur as a result of the change)

A. Change in operating parameter results in insufficient heating of containers leading to non-sterile product

B. Change in operating parameter results in insufficient heating of containers leading to product containing endotoxins

Severity of Event (S):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

A. **Major:** Has a substantial potential to have an adverse effect on the identity, strength, quality, purity or potency of a drug product **(4)**

B. **Major:** Has a substantial potential to have an adverse effect on the identity, strength, Quality, purity or potency of a drug product **(4)**

Frequency Estimation (F):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

A. **Highly Unlikely:** The probability of the event occurring is so low that it can be assumed that the event will not occur **(1)**

B. **Highly Unlikely:** The probability of the event occurring is so low that it can be assumed that the event will not occur **(1)**

Level of Detectability (D):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

A. **Readily Detectable:** Will be detected **(1)**

B. **Readily Detectable:** Will be detected **(1)**

Type of Data Needed to Support the Change:

- A. - Endotoxin reduction studies
- Temperature mapping studies

- B. - Endotoxin reduction studies
- Temperature mapping studies

Risk Level of Change Based on Assessment:

Event A

$$\begin{array}{c} \boxed{4} \\ (S) \end{array} \times \begin{array}{c} \boxed{1} \\ (F) \end{array} \times \begin{array}{c} \boxed{1} \\ (D) \end{array} = \begin{array}{c} \boxed{4} \\ \text{Risk Level} \end{array}$$

Event B

$$\begin{array}{c} \boxed{4} \\ (S) \end{array} \times \begin{array}{c} \boxed{1} \\ (F) \end{array} \times \begin{array}{c} \boxed{1} \\ (D) \end{array} = \begin{array}{c} \boxed{4} \\ \text{Risk Level} \end{array}$$

Overall Risk Level:

$$\boxed{4}$$

Risk Assessment #B7

Change Description in Detail:

Change in dry heat oven operating parameter for terminally sterilized product

Assumptions and Comments:

- Oven is used for depyrogenation and sterilization of glass product containers
- Containers being sterilized and depyrogenated are in covered trays or pans

Possible Events:

(Negative events that could occur as a result of the change)

- A Change in operating parameter results in insufficient heating of containers leading to product containing endotoxins

Severity of Event (S):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

- A. **Major:** Has a substantial potential to have an adverse effect on the identity, strength, quality, purity or potency of a drug product **(4)**

Frequency Estimation (F):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

- A. **Highly Unlikely:** The probability of the event occurring is so low that it can be assumed that the event will not occur **(1)**

Level of Detectability (D):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

- A. **Readily Detectable:** Will be detected **(1)**

Type of Data Needed to Support the Change:

- A. - Endotoxin reduction studies
- Temperature mapping studies

Risk Level of Change Based on Assessment:

Event A

$$\begin{array}{c} \boxed{4} \\ (S) \end{array} \times \begin{array}{c} \boxed{1} \\ (F) \end{array} \times \begin{array}{c} \boxed{1} \\ (D) \end{array} = \begin{array}{c} \boxed{4} \\ \text{Risk Level} \end{array}$$

Overall Risk Level:

4

Risk Assessment #B8

Change Description in Detail:

Change or addition of dry heat oven for aseptically produced product

Assumptions and Comments:

- Process prior to change uses dry heat oven(s)
- Oven is used for depyrogenation and sterilization of glass product containers
- Containers being sterilized and depyrogenated are in covered trays or pans

Possible Events:

(Negative events that could occur as a result of the change)

A. New oven performs differently resulting in insufficient heating of containers leading to non-sterile product

B. New oven performs differently from existing oven resulting in insufficient heating of containers leading to product containing endotoxins

Severity of Event (S):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

A. **Major:** Has a substantial potential to have an adverse effect on the identity, strength, quality, purity or potency of a drug product **(4)**

B. **Major:** Has a substantial potential to have an adverse effect on the identity, strength, quality, purity or potency of a drug product. **(4)**

Frequency Estimation (F):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

A. **Highly Unlikely:** The probability of the event occurring is so low that it can be assumed that the event will not occur **(1)**

B. **Highly Unlikely:** The probability of the event occurring is so low that it can be assumed that the event will not occur **(1)**

Level of Detectability (D):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

A. **Readily Detectable:** Will be detected **(1)**

B. **Readily Detectable:** Will be detected **(1)**

Type of Data Needed to Support the Change:

A. - Endotoxin reduction studies
- Temperature mapping studies.

B. - Endotoxin reduction studies
- Temperature mapping studies

Risk Level of Change Based on Assessment:

Event A

$$\begin{array}{c} \boxed{4} \\ (S) \end{array} \times \begin{array}{c} \boxed{1} \\ (F) \end{array} \times \begin{array}{c} \boxed{1} \\ (D) \end{array} = \begin{array}{c} \boxed{4} \\ \text{Risk Level} \end{array}$$

Event B

$$\begin{array}{c} \boxed{4} \\ (S) \end{array} \times \begin{array}{c} \boxed{1} \\ (F) \end{array} \times \begin{array}{c} \boxed{1} \\ (D) \end{array} = \begin{array}{c} \boxed{4} \\ \text{Risk Level} \end{array}$$

Overall Risk Level:

$$\boxed{4}$$

Risk Assessment #B9

Change Description in Detail:

Change or addition of dry heat oven for terminally sterilized product

Assumptions and Comments:

- Process prior to change uses dry heat oven(s)
- Oven used for depyrogenation and sterilization of glass product containers
- Containers being sterilized and depyrogenated are in covered trays or pans

Possible Events:

(Negative events that could occur as a result of the change)

- A. New oven performs differently from existing oven resulting in insufficient heating of containers leading to product containing endotoxins

Severity of Event (S):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

- A. **Major:** Has a substantial potential to have an adverse effect on the identity, strength, quality, purity or potency of a drug product **(4)**

Frequency Estimation (F):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

- A. **Highly Unlikely:** The probability of the event occurring is so low that it can be assumed that the event will not occur **(1)**

Level of Detectability (D):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

- A. **Readily Detectable:** Will be detected **(1)**

Type of Data Needed to Support the Change:

- A. - Endotoxin reduction studies
- Temperature mapping studies

Risk Level of Change Based on Assessment:

Event A

$$\begin{array}{c} \boxed{4} \\ (S) \end{array} \times \begin{array}{c} \boxed{1} \\ (F) \end{array} \times \begin{array}{c} \boxed{1} \\ (D) \end{array} = \begin{array}{c} \boxed{4} \\ \text{Risk Level} \end{array}$$

Overall Risk Level:

4

Risk Assessment #B10

Change Description in Detail:

Change in dry heat tunnel operating parameter for aseptically processed product

Assumptions and Comments:

- Process prior to change uses dry heat tunnel
- Tunnel used for depyrogenation and sterilization of glass product containers

Possible Events:

(Negative events that could occur as a result of the change)

A. Change in operating parameter results in insufficient heating of containers leading to non-sterile product

B. Change in operating parameter results in insufficient heating of containers leading to product containing endotoxins

C. Change in operating parameter results in a change in the differential pressure between the tunnel and the filling area causing a change in the airflow pattern over the filling line resulting in non-sterile product

Severity of Event (S):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

A. **Major:** Has a substantial potential to have an adverse effect on the identity, strength, quality, purity or potency of a drug product **(4)**

B. **Major:** Has a substantial potential to have an adverse effect on the identity, strength, quality, purity or potency of a drug product **(4)**

C. **Major:** Has a substantial potential to have an adverse effect on the identity, strength, quality, purity or potency of a drug product **(4)**

Frequency Estimation (F):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

A. **Highly Unlikely:** The probability of the event occurring is so low that it can be assumed that the event will not occur **(1)**

B. **Highly Unlikely:** The probability of the event occurring is so low that it can be assumed that the event will not occur **(1)**

C. **Likely:** Event may occur and/or has occurred in the past **(3)**

Level of Detectability (D):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

A. **Readily Detectable:** Will be detected **(1)**

B. **Readily Detectable:** Will be detected **(1)**

C. **Readily Detectable:** Will be detected (1)

Type of Data Needed to Support the Change:

A. - Endotoxin reduction studies
- Temperature mapping studies
- Media fills

B. - Endotoxin reduction studies
- Temperature mapping studies

C. - Air flow pattern testing
- Media fills

Risk Level of Change Based on Assessment:

Event A
$$\frac{4}{(S)} \times \frac{1}{(F)} \times \frac{1}{(D)} = \frac{4}{\text{Risk Level}}$$

Event B
$$\frac{4}{(S)} \times \frac{1}{(F)} \times \frac{1}{(D)} = \frac{4}{\text{Risk Level}}$$

Event C
$$\frac{4}{(S)} \times \frac{3}{(F)} \times \frac{1}{(D)} = \frac{12}{\text{Risk Level}}$$

Overall Risk Level:

12

Risk Assessment #B11

Change Description in Detail:

Change in dry heat tunnel operating parameter for terminally sterilized product

Assumptions and Comments:

- Process prior to change uses dry heat tunnel
- Tunnel used for depyrogenation and sterilization of glass product containers

Possible Events:

(Negative events that could occur as a result of the change)

- A. Change in operating parameter results in insufficient heating of containers leading to product containing endotoxins

Severity of Event (S):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

- A. **Major:** Has a substantial potential to have an adverse effect on the identity, strength, quality, purity or potency of a drug product **(4)**

Frequency Estimation (F):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

- A. **Highly Unlikely:** The probability of the event occurring is so low that it can be assumed that the event will not occur **(1)**

Level of Detectability (D):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

- A. **Readily Detectable:** Will be detected **(1)**

Type of Data Needed to Support the Change:

- A. - Endotoxin reduction studies
- Temperature mapping studies

Risk Level of Change Based on Assessment:

Event A

$$\begin{array}{c} \boxed{4} \\ (S) \end{array} \times \begin{array}{c} \boxed{1} \\ (F) \end{array} \times \begin{array}{c} \boxed{1} \\ (D) \end{array} = \begin{array}{c} \boxed{4} \\ \text{Risk Level} \end{array}$$

Overall Risk Level:

4

Risk Assessment #B12

Change Description in Detail:

Change in dry heat tunnel for aseptically processed product

Assumptions and Comments:

- Process prior to change uses dry heat tunnel
- Tunnel used for depyrogenation and sterilization of glass product containers
- Operating parameters have not changed

Possible Events:

(Negative events that could occur as a result of the change)

A. New tunnel performs differently than existing tunnel resulting in insufficient heating of containers leading to non-sterile product

B. New tunnel performs differently from existing tunnel resulting in insufficient heating of containers leading to product containing endotoxins

C. New tunnel performs differently from existing tunnel resulting in a change in the differential pressure between the tunnel and the filling area causing a change in the airflow pattern over the filling line resulting in non-sterile product

D. New tunnel's physical design (shape or function) results in changes in air flow patterns in the filling area causing a reduction in sterility assurance and resulting in non-sterile product

Severity of Event (S):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

A. **Major:** Has a substantial potential to have an adverse effect on the identity, strength, quality, purity or potency of a drug product **(4)**

B. **Major:** Has a substantial potential to have an adverse effect on the identity, strength, quality, purity or potency of a drug product **(4)**

C. **Major:** Has a substantial potential to have an adverse effect on the identity, strength, quality, purity or potency of a drug product **(4)**

D. **Major:** Has a substantial potential to have an adverse effect on the identity, strength, quality, purity or potency of a drug product **(4)**

Frequency Estimation (F):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

A. **Highly Unlikely:** The probability of the event occurring is so low that it can be assumed that the event will not occur **(1)**

B. **Highly Unlikely:** The probability of the event occurring is so low that it can be assumed that the event will not occur **(1)**

C. **Likely:** Event may occur and/or has occurred in the past **(3)**

D. **Likely:** Event may occur and/or has occurred in the past **(3)**

Level of Detectability (D):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

A. **Readily Detectable:** Will be detected **(1)**

B. **Readily Detectable:** Will be detected **(1)**

C. **Readily Detectable:** Will be detected **(1)**

D. **Readily Detectable:** Will be detected **(1)**

Type of Data Needed to Support the Change:

A. - Endotoxin reduction studies
- Temperature mapping studies
- Media fills

B. - Endotoxin reduction studies
- Temperature mapping studies

C. - Air flow pattern testing
- Media fills

D. - Air flow pattern testing
- Media fills

Risk Level of Change Based on Assessment:

Event A

$$\begin{array}{c} \boxed{4} \\ (S) \end{array} \times \begin{array}{c} \boxed{1} \\ (F) \end{array} \times \begin{array}{c} \boxed{1} \\ (D) \end{array} = \begin{array}{c} \boxed{4} \\ \text{Risk Level} \end{array}$$

Event B

$$\begin{array}{c} \boxed{4} \\ (S) \end{array} \times \begin{array}{c} \boxed{1} \\ (F) \end{array} \times \begin{array}{c} \boxed{1} \\ (D) \end{array} = \begin{array}{c} \boxed{4} \\ \text{Risk Level} \end{array}$$

Event C

$$\begin{array}{c} \boxed{4} \\ (S) \end{array} \times \begin{array}{c} \boxed{3} \\ (F) \end{array} \times \begin{array}{c} \boxed{1} \\ (D) \end{array} = \begin{array}{c} \boxed{12} \\ \text{Risk Level} \end{array}$$

Event D

$$\begin{array}{c} \boxed{4} \\ (S) \end{array} \times \begin{array}{c} \boxed{3} \\ (F) \end{array} \times \begin{array}{c} \boxed{1} \\ (D) \end{array} = \begin{array}{c} \boxed{12} \\ \text{Risk Level} \end{array}$$

Overall Risk Level:

$\boxed{12}$

Risk Assessment #B13

Change Description in Detail:

Change in dry heat tunnel for terminally sterilized product

Assumptions and Comments:

- Process prior to change uses dry heat tunnel
- Tunnel used for depyrogenation and sterilization of glass product containers
- Operating parameters have not changed

Possible Events:

(Negative events that could occur as a result of the change)

- A. New tunnel performs differently from existing tunnel resulting in insufficient heating of containers leading to product containing endotoxins

Severity of Event (S):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

- A. **Major:** Has a substantial potential to have an adverse effect on the identity, strength, quality, purity or potency of a drug product **(4)**

Frequency Estimation (F):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

- A. **Highly Unlikely:** The probability of the event occurring is so low that it can be assumed that the event will not occur **(1)**

Level of Detectability (D):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

- A. **Readily Detectable:** Will be detected **(1)**

Type of Data Needed to Support the Change:

- A. - Endotoxin reduction studies
- Temperature mapping studies

Risk Level of Change Based on Assessment:

Event A

$$\begin{array}{c} \boxed{4} \\ (S) \end{array} \times \begin{array}{c} \boxed{1} \\ (F) \end{array} \times \begin{array}{c} \boxed{1} \\ (D) \end{array} = \begin{array}{c} \boxed{4} \\ \text{Risk Level} \end{array}$$

Overall Risk Level:

4

Risk Assessment #B14

Change Description in Detail:

Change in sterile and other filters; Different membrane, different filter, different housing

Assumptions and Comments:

- None

Possible Events:

(Negative events that could occur as a result of the change)

A. Product/excipient absorbed onto membrane impacting the potency or stability of the product

B. Product extracts materials from membrane causing product to be contaminated

C. Product incompatible with membrane (reacts with membrane) adversely impacting product potency or stability

D. Microorganisms not removed from the product resulting in non-sterile product

E. Shift in product bubble point resulting in inaccurate integrity test results potentially resulting in non-sterile product

Severity of Event (S):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

A. **Moderate:** Has a moderate potential to have an adverse effect on the identity, strength, quality, purity or potency of a drug product **(3)**

B. **Moderate:** Has a moderate potential to have an adverse effect on the identity, strength, quality, purity or potency of a drug product **(3)**

C. **Moderate:** Has a moderate potential to have an adverse effect on the identity, strength, quality, purity or potency of a drug product **(3)**

D. **Major:** Has a substantial potential to have an adverse effect on the identity, strength, quality, purity or potency of a drug product **(4)**

E. **Major:** Has a substantial potential to have an adverse effect on the identity, strength, quality, purity or potency of a drug product **(4)**

Frequency Estimation (F):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

A. **Unlikely:** Event not expected to occur, but theoretically possible **(2)**

B. **Unlikely:** Event not expected to occur, but theoretically possible **(2)**

C. **Unlikely:** Event not expected to occur, but theoretically possible **(2)**

D. **Likely:** Event may occur and/or has occurred in the past **(3)**

E. **Unlikely:** Event not expected to occur, but theoretically possible **(2)**

Level of Detectability (D):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

A. **Readily Detectable:** Will be detected (1)

B. **Readily Detectable:** Will be detected (1)

C. **Readily Detectable:** Will be detected (1)

D. **Readily Detectable:** Will be detected (1)

E. **Readily Detectable:** Will be detected (1)

Type of Data Needed to Support the Change:

A. - Chemical assay and stability data (extractability, compatibility, and analytical testing to support the validation studies)

B. - Chemical assay and stability data (extractability, compatibility, and analytical testing to support the validation studies)

C. - Chemical assay and stability data (extractability, compatibility, and analytical testing to support the validation studies)

D. - Microbial retention studies

E. - Filter validation
- Integrity testing

Risk Level of Change Based on Assessment:

(Use the largest value from each factor section (i.e. if under Severity (S) there were three event values obtained (2, 3, 4) the highest value (4) should be used in the calculation)).

Event A

$$\begin{array}{c} \boxed{3} \\ (S) \end{array} \times \begin{array}{c} \boxed{2} \\ (F) \end{array} \times \begin{array}{c} \boxed{1} \\ (D) \end{array} = \begin{array}{c} \boxed{6} \\ \text{Risk Level} \end{array}$$

Event B

$$\begin{array}{c} \boxed{3} \\ (S) \end{array} \times \begin{array}{c} \boxed{2} \\ (F) \end{array} \times \begin{array}{c} \boxed{1} \\ (D) \end{array} = \begin{array}{c} \boxed{6} \\ \text{Risk Level} \end{array}$$

Event C

$$\begin{array}{c} \boxed{3} \\ (S) \end{array} \times \begin{array}{c} \boxed{2} \\ (F) \end{array} \times \begin{array}{c} \boxed{1} \\ (D) \end{array} = \begin{array}{c} \boxed{6} \\ \text{Risk Level} \end{array}$$

Event D

$$\begin{array}{c} \boxed{4} \\ (S) \end{array} \times \begin{array}{c} \boxed{3} \\ (F) \end{array} \times \begin{array}{c} \boxed{1} \\ (D) \end{array} = \begin{array}{c} \boxed{12} \\ \text{Risk Level} \end{array}$$

Event E

$$\begin{array}{c} \boxed{4} \\ (S) \end{array} \times \begin{array}{c} \boxed{2} \\ (F) \end{array} \times \begin{array}{c} \boxed{1} \\ (D) \end{array} = \begin{array}{c} \boxed{8} \\ \text{Risk Level} \end{array}$$

Overall Risk Level:

$$\boxed{12}$$

Risk Assessment #B15

Change Description in Detail:

Change in sterile and other filters
- Change in operating parameters outside validation
- Change in filter pore size resulting in change in operating parameters

Assumptions and Comments:

- Change is in the filtration operating parameters (i.e. pressure, flow rate, etc.)

Possible Events:

(Negative events that could occur as a result of the change)

A. Microorganisms not removed (filter intact) resulting in non sterile product

B. Membrane/cartridge damaged as result of parameter change resulting in non-sterile product

Severity of Event (S):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

A. **Major:** Has a substantial potential to have an adverse effect on the identity, strength, quality, purity or potency of a drug product **(4)**

B. **Major:** Has a substantial potential to have an adverse effect on the identity, strength, quality, purity or potency of a drug product **(4)**

Frequency Estimation (F):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

A. **Likely:** Event may occur and/or has occurred in the past **(3)**

B. **Likely:** Event may occur and/or has occurred in the past **(3)**

Level of Detectability (D):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

A. **Readily Detectable:** Will be detected **(1)**

B. **Readily Detectable:** Will be detected **(1)**

Type of Data Needed to Support the Change:

A. Microbial retention studies

B. Filter validation
Integrity testing

Risk Level of Change Based on Assessment:

Event A

$$\begin{array}{c} \boxed{4} \\ (S) \end{array} \times \begin{array}{c} \boxed{3} \\ (F) \end{array} \times \begin{array}{c} \boxed{1} \\ (D) \end{array} = \begin{array}{c} \boxed{12} \\ \text{Risk Level} \end{array}$$

Event B

$$\begin{array}{c} \boxed{4} \\ \text{(S)} \end{array} \times \begin{array}{c} \boxed{3} \\ \text{(F)} \end{array} \times \begin{array}{c} \boxed{1} \\ \text{(D)} \end{array} = \begin{array}{c} \boxed{12} \\ \text{Risk Level} \end{array}$$

Overall Risk Level:

$$\boxed{12}$$

Risk Assessment #C1

Change Description in Detail:

Increase in batch size for aseptically filled product

Assumptions and Comments:

- No change in equipment, i.e. mixing tanks, piping, filter housings, and subsequent processing equipment, such as fillers

Possible Events:

(Negative events that could occur as a result of the change)

A. Increased bioburden leading to non-sterile product (if hold time is increased)

B. Increase in endotoxins leading to product contaminated with endotoxins (if hold time is increased)

C. Lack of product homogeneity due to improper mixing

Severity of Event (S):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

A. **Major:** Has a substantial potential to have an adverse effect on the identity, strength, quality, purity or potency of a drug product **(4)**

B. **Major:** Has a substantial potential to have an adverse effect on the identity, strength, quality, purity or potency of a drug product **(4)**

C. **Major:** Has a substantial potential to have an adverse effect on the identity, strength, quality, purity or potency of a drug product **(4)**

Frequency Estimation (F):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

A. **Unlikely:** Event not expected to occur, but theoretically possible **(2)**

B. **Unlikely:** Event not expected to occur, but theoretically possible **(2)**

C. **Unlikely:** Event not expected to occur, but theoretically possible **(2)**

Level of Detectability (D):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

A. **Readily Detectable:** Will be detected **(1)**

B. **Readily Detectable:** Will be detected **(1)**

C. **Readily Detectable:** Will be detected **(1)**

Type of Data Needed to Support the Change:

A. - Microbiological hold time studies if hold times are increased
- Media fill

B. - Hold time studies for endotoxin if hold times are increased

C. - Mixing validation (for emulsions or other products that require specific particle size requirements, these must be included in the mixing validation)
- Chemical hold time studies

Risk Level of Change Based on Assessment:

Event A

$$\frac{4}{(S)} \times \frac{2}{(F)} \times \frac{1}{(D)} = \frac{8}{\text{Risk Level}}$$

Event B

$$\frac{4}{(S)} \times \frac{2}{(F)} \times \frac{1}{(D)} = \frac{8}{\text{Risk Level}}$$

Event C

$$\frac{4}{(S)} \times \frac{2}{(F)} \times \frac{1}{(D)} = \frac{8}{\text{Risk Level}}$$

Overall Risk Level:

8

Risk Assessment #C2

Change Description in Detail:

Increase in batch size for terminally sterilized product

Assumptions and Comments:

- No change in equipment, i.e. mixing tanks, piping, filter housings, and subsequent processing equipment, such as fillers

Possible Events:

(Negative events that could occur as a result of the change)

A. Increased bioburden leading to non-sterile product (if hold time is increased)

B. Increase in endotoxins leading to product contaminated with endotoxins (if hold time is increased)

C. Lack of product homogeneity due to improper mixing

Severity of Event (S):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

A. **Major:** Has a substantial potential to have an adverse effect on the identity, strength, quality, purity or potency of a drug product **(4)**

B. **Major:** Has a substantial potential to have an adverse effect on the identity, strength, quality, purity or potency of a drug product **(4)**

C. **Major:** Has a substantial potential to have an adverse effect on the identity, strength, quality, purity or potency of a drug product **(4)**

Frequency Estimation (F):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

A. **Unlikely:** Event not expected to occur, but theoretically possible **(2)**

B. **Unlikely:** Event not expected to occur, but theoretically possible **(2)**

C. **Unlikely:** Event not expected to occur, but theoretically possible **(2)**

Level of Detectability (D):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

A. **Readily Detectable:** Will be detected **(1)**

B. **Readily Detectable:** Will be detected **(1)**

C. **Readily Detectable:** Will be detected **(1)**

Type of Data Needed to Support the Change:

A. - Microbiological hold time studies if hold times are increased
- Sterilization validation of new lot size (if applicable)

B. - Hold time studies for endotoxin if hold times are increased

C. - Mixing validation (For emulsions or other products that require specific particle size requirements, these must be included in the mixing validation)
- Chemical hold time studies

Risk Level of Change Based on Assessment:

Event A
 $\begin{array}{c} \boxed{4} \\ (S) \end{array} \times \begin{array}{c} \boxed{2} \\ (F) \end{array} \times \begin{array}{c} \boxed{1} \\ (D) \end{array} = \begin{array}{c} \boxed{8} \\ \text{Risk Level} \end{array}$

Event B
 $\begin{array}{c} \boxed{4} \\ (S) \end{array} \times \begin{array}{c} \boxed{2} \\ (F) \end{array} \times \begin{array}{c} \boxed{1} \\ (D) \end{array} = \begin{array}{c} \boxed{8} \\ \text{Risk Level} \end{array}$

Event C
 $\begin{array}{c} \boxed{4} \\ (S) \end{array} \times \begin{array}{c} \boxed{2} \\ (F) \end{array} \times \begin{array}{c} \boxed{1} \\ (D) \end{array} = \begin{array}{c} \boxed{8} \\ \text{Risk Level} \end{array}$

Overall Risk Level:

$\boxed{8}$

Risk Assessment #C3

Change Description in Detail:

Change in preparation (washing/siliconization/use of 3rd Party) of elastomeric closures, prior to their sterilization or change to use "ready-to-sterilize" closures for aseptically processed products

Assumptions and Comments:

- There are changes to stopper washing process parameters
- There are no changes to the stopper sterilization cycle

Possible Events:

(Negative events that could occur as a result of the change)

A. Closures have a high level of endotoxins present, washing with a different process causes the final product to be contaminated with endotoxins

B. Closures washed with a different process have residual detergent present causing the final product to be contaminated with detergent

C. Closures washed with a different process have a high particulate load causing the final product to be contaminated with particulates

D. Closures have a non-optimal siliconization impacting the manufacturing performance and possibly leading to the production of non-sterile products

E. For protein products, over-siliconization of closures results in aggregation of proteins resulting in product with visible particulates and reduced potency

Severity of Event (S):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

A. **Major:** Has a substantial potential to have an adverse effect on the identity, strength, quality, purity or potency of a drug product **(4)**

B. **Moderate:** Has a moderate potential to have an adverse effect on the identity, strength, quality, purity or potency of a drug product **(3)**

C. **Moderate:** Has a moderate potential to have an adverse effect on the identity, strength, quality, purity or potency of a drug product **(3)**

D. **Major:** Has a substantial potential to have an adverse effect on the identity, strength, quality, purity or potency of a drug product **(4)**

E. **Major:** Has a substantial potential to have an adverse effect on the identity, strength, quality, purity or potency of a drug product **(4)**

Frequency Estimation (F):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

A. **Unlikely:** Event not expected to occur, but theoretically possible **(2)**

B. **Unlikely:** Event not expected to occur, but theoretically possible **(2)**

C. **Unlikely:** Event not expected to occur, but theoretically possible (2)

D. **Likely:** Event may occur and/or has occurred in the past (3)

E. **Likely:** Event may occur and/or has occurred in the past (3)

Level of Detectability (D):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

A. **Readily Detectable:** Will be detected using the methods performed (1)

B. **Readily Detectable:** Will be detected using the methods performed (1)

C. **Readily Detectable:** Will be detected using the methods performed (1)

D. **Readily Detectable:** Will be detected using the methods performed (1)

E. **Readily Detectable:** Will be detected using the methods performed (1)

Type of Data Needed to Support the Change:

A. Endotoxin reduction validation

B. Cleaning agent residue validation

C. Particulate load testing

D. Machineability and media fill

E. Siliconization studies

Risk Level of Change Based on Assessment:

Event A

$$\begin{array}{c} \boxed{4} \\ (S) \end{array} \times \begin{array}{c} \boxed{2} \\ (F) \end{array} \times \begin{array}{c} \boxed{1} \\ (D) \end{array} = \begin{array}{c} \boxed{8} \\ \text{Risk Level} \end{array}$$

Event B

$$\begin{array}{c} \boxed{3} \\ (S) \end{array} \times \begin{array}{c} \boxed{2} \\ (F) \end{array} \times \begin{array}{c} \boxed{1} \\ (D) \end{array} = \begin{array}{c} \boxed{6} \\ \text{Risk Level} \end{array}$$

Event C

$$\begin{array}{c} \boxed{3} \\ (S) \end{array} \times \begin{array}{c} \boxed{2} \\ (F) \end{array} \times \begin{array}{c} \boxed{1} \\ (D) \end{array} = \begin{array}{c} \boxed{6} \\ \text{Risk Level} \end{array}$$

Event D

$$\begin{array}{c} \boxed{4} \\ (S) \end{array} \times \begin{array}{c} \boxed{3} \\ (F) \end{array} \times \begin{array}{c} \boxed{1} \\ (D) \end{array} = \begin{array}{c} \boxed{12} \\ \text{Risk Level} \end{array}$$

Event E

$$\begin{array}{c} \boxed{4} \\ (S) \end{array} \times \begin{array}{c} \boxed{3} \\ (F) \end{array} \times \begin{array}{c} \boxed{1} \\ (D) \end{array} = \begin{array}{c} \boxed{12} \\ \text{Risk Level} \end{array}$$

Overall Risk Level:

$\boxed{12}$

Risk Assessment #C4

Change Description in Detail:

Change in preparation (washing/siliconization/use of 3rd Party) of elastomeric closures, prior to their sterilization or change to use "ready-to-sterilize" closures for terminally sterilized product

Assumptions and Comments:

- There are changes to stopper washing process parameters
- There are no changes to the stopper sterilization cycle

Possible Events:

(Negative events that could occur as a result of the change)

A. Closures have a high level of endotoxins present, washing with a different process causes the final product to be contaminated with endotoxins

B. Closures washed with a different process have residual detergent present causing the final product to be contaminated with detergent

C. Closures washed with a different process have a high particulate load causing the final product to be contaminated with particulates

Severity of Event (S):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

A. **Major:** Has a substantial potential to have an adverse effect on the identity, strength, quality, purity or potency of a drug product **(4)**

B. **Moderate:** Has a moderate potential to have an adverse effect on the identity, strength, quality, purity or potency of a drug product **(3)**

C. **Moderate:** Has a moderate potential to have an adverse effect on the identity, strength, quality, purity or potency of a drug product **(3)**

Frequency Estimation (F):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

A. **Unlikely:** Event not expected to occur, but theoretically possible **(2)**

B. **Unlikely:** Event not expected to occur, but theoretically possible **(2)**

C. **Unlikely:** Event not expected to occur, but theoretically possible **(2)**

Level of Detectability (D):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

A. **Readily Detectable:** Will be detected **(1)**

B. **Readily Detectable:** Will be detected **(1)**

C. **Readily Detectable:** Will be detected **(1)**

Type of Data Needed to Support the Change:

A. Endotoxin reduction validation

B. Cleaning agent residue validation

C. Particulate load testing

Risk Level of Change Based on Assessment:

Event A

$$\frac{4}{(S)} \times \frac{2}{(F)} \times \frac{1}{(D)} = \frac{8}{\text{Risk Level}}$$

Event B

$$\frac{3}{(S)} \times \frac{2}{(F)} \times \frac{1}{(D)} = \frac{6}{\text{Risk Level}}$$

Event C

$$\frac{3}{(S)} \times \frac{2}{(F)} \times \frac{1}{(D)} = \frac{6}{\text{Risk Level}}$$

Overall Risk Level:

8

Risk Assessment #C5

Change Description in Detail:

Change in filtration duration (increase)

Assumptions and Comments:

- No other changes to filter or batch size
- For aseptically processed and terminally sterilized products

Possible Events:

(Negative events that could occur as a result of the change)

A. Increase in the time the product is in contact with the filter results in an increase in extractables/leachables in the drug product

B. Increase in the time the product is in contact with the filter results in product being absorbed causing a reduction in drug product potency

C. Increase in the filtration duration causes an elevated bulk bioburden and/or endotoxins level leading to an increase in endotoxins contamination and non-sterile drug product

Severity of Event (S):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

A. **Major:** Has a substantial potential to have an adverse effect on the identity, strength, quality, purity or potency of a drug product **(4)**

B. **Major:** Has a substantial potential to have an adverse effect on the identity, strength, quality, purity or potency of a drug product **(4)**

C. **Major:** Has a substantial potential to have an adverse effect on the identity, strength, quality, purity or potency of a drug product **(4)**

Frequency Estimation (F):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

A. **Unlikely:** Event not expected to occur, but theoretically possible **(2)**

B. **Unlikely:** Event not expected to occur, but theoretically possible **(2)**

C. **Unlikely:** Event not expected to occur, but theoretically possible **(2)**

Level of Detectability (D):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

A. **Readily Detectable:** Will be detected **(1)**

B. **Readily Detectable:** Will be detected **(1)**

C. **Readily Detectable:** Will be detected **(1)**

Type of Data Needed to Support the Change:

A. - Process validation (media fill, extractable profile, flow decay, filter flush and downtime, change in filtration time)
- Stability data

B. - Process validation (media fill, extractable profile, flow decay, filter flush and downtime, change in filtration time)
- Stability data

C. - Media fill
- Endotoxin testing of the bulk

Risk Level of Change Based on Assessment:

Event A

$$\begin{array}{c} \boxed{4} \\ (S) \end{array} \times \begin{array}{c} \boxed{2} \\ (F) \end{array} \times \begin{array}{c} \boxed{1} \\ (D) \end{array} = \begin{array}{c} \boxed{8} \\ \text{Risk Level} \end{array}$$

Event B

$$\begin{array}{c} \boxed{4} \\ (S) \end{array} \times \begin{array}{c} \boxed{2} \\ (F) \end{array} \times \begin{array}{c} \boxed{1} \\ (D) \end{array} = \begin{array}{c} \boxed{8} \\ \text{Risk Level} \end{array}$$

Event C

$$\begin{array}{c} \boxed{4} \\ (S) \end{array} \times \begin{array}{c} \boxed{2} \\ (F) \end{array} \times \begin{array}{c} \boxed{1} \\ (D) \end{array} = \begin{array}{c} \boxed{8} \\ \text{Risk Level} \end{array}$$

Overall Risk Level:

$$\boxed{8}$$

Risk Assessment #C6

Change Description in Detail:

Change in number of sterilizing filters (increase)

Assumptions and Comments:

- Increase in the number of the same type of sterilizing filters
- Aseptically processed and terminally sterilized products

Possible Events:

(Negative events that could occur as a result of the change)

A. Increase in the number of filters (and therefore product exposure to the filter components) leads to an increase in the level of extractables/leachables in the drug product

B. Increase in the number of filters (and therefore product exposure to the filter components) leads to a reduction of drug product potency due to increased product absorption

Severity of Event (S):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

A. **Major:** Has a substantial potential to have an adverse effect on the identity, strength, quality, purity or potency of a drug product **(4)**

B. **Major:** Has a substantial potential to have an adverse effect on the identity, strength, quality, purity or potency of a drug product **(4)**

Frequency Estimation (F):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

A. **Unlikely:** Event not expected to occur, but theoretically possible **(2)**

B. **Unlikely:** Event not expected to occur, but theoretically possible **(2)**

Level of Detectability (D):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

A. **Readily Detectable:** Will be detected **(1)**

B. **Readily Detectable:** Will be detected **(1)**

Type of Data Needed to Support the Change:

A. - Process validation (media fill, extractable profile, flow decay, filter flush and downtime, change in filtration time)
- Stability data

B. - Process validation (media fill, extractable profile, flow decay, filter flush and downtime, change in filtration time)
- Stability data

Risk Level of Change Based on Assessment:

Event A

$$\frac{4}{(S)} \times \frac{2}{(F)} \times \frac{1}{(D)} = \frac{8}{\text{Risk Level}}$$

Event B

$$\frac{4}{(S)} \times \frac{2}{(F)} \times \frac{1}{(D)} = \frac{8}{\text{Risk Level}}$$

Overall Risk Level:

$$\frac{8}{}$$

Risk Assessment #C7

Change Description in Detail:

Change in lyophilization parameters

Assumptions and Comments:

No change in equipment (same design and operating principles)

Possible Events:

(Negative events that could occur as a result of the change)

A. Change in parameters of existing validated cycle changes the validated freeze drying cycle and causes improper cake formation, excess moisture or excessive reconstitution times

Severity of Event (S):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

A. **Major:** Has a substantial potential to have an adverse effect on the identity, strength, quality, purity or potency of a drug product **(4)**

Frequency Estimation (F):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

A. **Highly Likely:** Event expected to occur **(4)**

Level of Detectability (D):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

A. **Readily Detectable:** Will be detected **(1)**

Type of Data Needed to Support the Change:

A. - Lyophilization validation data
- Stability data

Risk Level of Change Based on Assessment:

Event A

$$\begin{array}{c} \boxed{4} \\ (S) \end{array} \times \begin{array}{c} \boxed{4} \\ (F) \end{array} \times \begin{array}{c} \boxed{1} \\ (D) \end{array} = \begin{array}{c} \boxed{16} \\ \text{Risk Level} \end{array}$$

Overall Risk Level:

16

Risk Assessment #C8

Change Description in Detail:

Change in lyophilizer pattern loading

Assumptions and Comments:

- Change in size or placement of existing validated load pattern

Possible Events:

(Negative events that could occur as a result of the change)

A. Change in size and placement of existing validated load pattern changes the validated freeze drying cycle and causes improper cake formation, excess moisture or excessive reconstitution times

Severity of Event (S):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

A. **Major:** Has a substantial potential to have an adverse effect on the identity, strength, quality, purity or potency of a drug product **(4)**

Frequency Estimation (F):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

A. **Likely:** Event may occur and/or has occurred in the past **(3)**

Level of Detectability (D):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

A. **Readily Detectable:** Will be detected **(1)**

Type of Data Needed to Support the Change:

A. - Lyophilization validation data
- Stability data

Risk Level of Change Based on Assessment:

Event A

$$\begin{array}{c} \boxed{4} \\ (S) \end{array} \times \begin{array}{c} \boxed{3} \\ (F) \end{array} \times \begin{array}{c} \boxed{1} \\ (D) \end{array} = \begin{array}{c} \boxed{12} \\ \text{Risk Level} \end{array}$$

Overall Risk Level:

12

Risk Assessment #C9

Change Description in Detail:

Change in sterilization loading pattern for fluid path product contact equipment and components for aseptically processed products

Assumptions and Comments:

- Change in size (increase) or loading orientation of existing validated sterilizer load

Possible Events:

(Negative events that could occur as a result of the change)

A. Change in equipment or component load pattern changes the heat distribution of the validated cycle resulting in non-sterile product

B. Changes in loading patterns results in wet loads. The resulting condensate impacts the sterility assurance of the product contact equipment resulting in non-sterile product

C. Changes in loading patterns results in wet loads. The condensate has a negative impact on the chemical /physical characteristics of the final product.

Severity of Event (S):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

A. **Major:** Has a substantial potential to have an adverse effect on the identity, strength, quality, purity or potency of a drug product **(4)**

B. **Major:** Has a substantial potential to have an adverse effect on the identity, strength, quality, purity or potency of a drug product **(4)**

C. **Moderate:** Has a moderate potential to have an adverse effect on the identity, strength, quality, purity or potency of a drug product **(3)**

Frequency Estimation (F):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

A. **Likely:** Event may occur and/or has occurred in the past **(3)**

B. **Likely:** Event may occur and/or has occurred in the past **(3)**

C. **Likely:** Event may occur and/or has occurred in the past **(3)**

Level of Detectability (D):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

A. **Readily Detectable:** Will be detected **(1)**

B. **Readily Detectable:** Will be detected (1)

C. **Readily Detectable:** Will be detected (1)

Type of Data Needed to Support the Change:

A. - Sterilization validation

B. - Sterilization validation

C. - Sterilization validation

Risk Level of Change Based on Assessment:

Event A

$$\frac{4}{(S)} \times \frac{3}{(F)} \times \frac{1}{(D)} = \frac{12}{\text{Risk Level}}$$

Event B

$$\frac{4}{(S)} \times \frac{3}{(F)} \times \frac{1}{(D)} = \frac{12}{\text{Risk Level}}$$

Event C

$$\frac{3}{(S)} \times \frac{3}{(F)} \times \frac{1}{(D)} = \frac{9}{\text{Risk Level}}$$

Overall Risk Level:

12

Risk Assessment #C10

Change Description in Detail:

Change in sterilization loading pattern for terminally sterilized finished products

Assumptions and Comments:

- Change in size (increase) or loading pattern of existing validated sterilizer load

Possible Events:

(Negative events that could occur as a result of the change)

A. Change in load pattern changes the heat penetration of the validated cycle resulting in inadequate sterilization of the finished product

Severity of Event (S):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

A. **Major:** Has a substantial potential to have an adverse effect on the identity, strength, quality, purity or potency of a drug product **(4)**

Frequency Estimation (F):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

A. **Likely:** Event may occur and/or has occurred in the past **(3)**

Level of Detectability (D):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

A. **Readily Detectable:** Will be detected **(1)**

Type of Data Needed to Support the Change:

A. - Sterilization validation

Risk Level of Change Based on Assessment:

Event A

4	x	3	x	1	=	12
(S)		(F)		(D)		Risk Level

Overall Risk Level:

12

Risk Assessment #C11

Change Description in Detail:

Change in the method of sterilization (fluid path product contact equipment, components, and finished product)

Assumptions and Comments:

- For aseptic and terminally sterilized products
- Excludes chemical sterilization (ethylene oxide, hydrogen peroxide, peracetic acid)

Possible Events:

(Negative events that could occur as a result of the change)

A. Contaminated equipment, components or finished products that could lead to the production of non-sterile product

B. Degradation of products or components by new method of sterilization or changes in the method parameters

Severity of Event (S):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

A. **Major:** Has a substantial potential to have an adverse effect on the identity, strength, quality, purity or potency of a drug product **(4)**

B. **Moderate:** Has a moderate potential to have an adverse effect on the identity, strength, quality, purity or potency of a drug product **(3)**

Frequency Estimation (F):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

A. **Likely:** Event may occur and/or has occurred in the past **(3)**

B. **Unlikely:** Event not expected to occur, but theoretically possible **(2)**

Level of Detectability (D):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

A. **May Be Detectable:** May be detected **(2)**

B. **May Be Detectable:** May be detected **(2)**

Type of Data Needed to Support the Change:

A. - Sterilization validation
- Media fill

B. - Assessment of new sterilization method impact (final product release and stability data) on product or components

Risk Level of Change Based on Assessment:

Event A

$$\frac{4}{(S)} \times \frac{3}{(F)} \times \frac{2}{(D)} = \frac{24}{\text{Risk Level}}$$

Event B

$$\frac{3}{(S)} \times \frac{2}{(F)} \times \frac{2}{(D)} = \frac{12}{\text{Risk Level}}$$

Overall Risk Level:

$$\frac{24}{}$$

Risk Assessments Format #C12

Change Description in Detail:

Change in sterilization cycle parameters within the existing method (fluid path product contact equipment, components, finished product)

Assumptions and Comments:

- For aseptically processed and terminally sterilized products
- Excludes chemical sterilization (ethylene oxide, hydrogen peroxide, peracetic acid)

Possible Events:

(Negative events that could occur as a result of the change)

A. Contaminated equipment, components or finished products leads to the production of non-sterile product

B. Degradation of products or components occurs due to changes in the method parameters

Severity of Event (S):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

A. **Major:** Has a substantial potential to have an adverse effect on the identity, strength, quality, purity or potency of a drug product **(4)**

B. **Moderate:** Has a moderate potential to have an adverse effect on the identity, strength, quality, purity or potency of a drug product **(3)**

Frequency Estimation (F):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

A. **Likely:** Event may occur and/or has occurred in the past **(3)**

B. **Unlikely:** Event not expected to occur, but theoretically possible **(2)**

Level of Detectability (D):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

A. **May Be Detectable:** May be detected **(2)**

B. **May Be Detectable:** May be detected **(2)**

Type of Data Needed to Support the Change:

- A. - Sterilization validation
- Media fill

- B. - Assessment of new sterilization method impact (final product release and stability data) on product or components

Risk Level of Change Based on Assessment:

Event A

$$\frac{4}{(S)} \times \frac{3}{(F)} \times \frac{2}{(D)} = \frac{24}{\text{Risk Level}}$$

Event B

$$\frac{3}{(S)} \times \frac{2}{(F)} \times \frac{2}{(D)} = \frac{12}{\text{Risk Level}}$$

Overall Risk Level:

$$\frac{24}{}$$

Risk Assessments #C13

Change Description in Detail:

Changes in compounding mixing speed

Assumptions and Comments:

- There are no changes in the ingredients
- Same type of equipment (same design and operating principles)
- The formulation is a true solution

Possible Events:

(Negative events that could occur as a result of the change)

- A. As a result of the mixing speed change drug product stability is negatively impacted (i.e. degradation of product, formation of product aggregates, discoloration, etc.)

Severity of Event (S):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

- A. **Moderate:** Has a moderate potential to have an adverse effect on the identity, strength, quality, purity or potency of a drug product **(3)**

Frequency Estimation (F):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

- A. **Unlikely:** Event not expected to occur, but theoretically possible **(2)**

Level of Detectability (D):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

- A. **Readily Detectable:** Will be detected **(1)**

Type of Data Needed to Support the Change:

- A. - Process validation
- Stability data

Risk Level of Change Based on Assessment:

Event A

$$\begin{array}{c} \boxed{3} \\ (S) \end{array} \times \begin{array}{c} \boxed{2} \\ (F) \end{array} \times \begin{array}{c} \boxed{1} \\ (D) \end{array} = \begin{array}{c} \boxed{6} \\ \text{Risk Level} \end{array}$$

Overall Risk Level:

6

Risk Assessments #C14

Change Description in Detail:

Changes in the order of addition of ingredients during compounding

Assumptions and Comments:

- There are no changes in the ingredients
- The formulation is a true solution

Possible Events:

(Negative events that could occur as a result of the change)

- A. As a result of change in the order of ingredient addition the drug product stability is negatively impacted (i.e. degradation of product, formation of product aggregates, discoloration, etc.)

Severity of Event (S):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

- A. **Moderate:** Has a moderate potential to have an adverse effect on the identity, strength, quality, purity or potency of a drug product **(3)**

Frequency Estimation (F):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

- A. **Unlikely:** Event not expected to occur, but theoretically possible **(2)**

Level of Detectability (D):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

- A. **Readily Detectable:** Will be detected **(1)**

Type of Data Needed to Support the Change:

- A. - Process validation
- Stability data

Risk Level of Change Based on Assessment:

Event A

$$\begin{array}{c} \boxed{3} \\ (S) \end{array} \times \begin{array}{c} \boxed{2} \\ (F) \end{array} \times \begin{array}{c} \boxed{1} \\ (D) \end{array} = \begin{array}{c} \boxed{6} \\ \text{Risk Level} \end{array}$$

Overall Risk Level:

6

Risk Assessments #C15

Change Description in Detail:

Change in time limits (increase) for pre-sterilization hold times (for processing steps including component preparation)

Assumptions and Comments:

- No equipment changes
- No other process changes
- Solutions are growth promoting

Possible Events:

(Negative events that could occur as a result of the change)

A. Increase in bioburden results in increased levels of endotoxins in the drug product

B. Increase in bioburden results in degradation of drug leading to increased impurity levels or a decrease in the potency of the drug product

C. Increase in bioburden results in production of a non-sterile drug product

Severity of Event (S):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

A. **Major:** Has a substantial potential to have an adverse effect on the identity, strength, quality, purity or potency of a drug product **(4)**

B. **Moderate:** Has a moderate potential to have an adverse effect on the identity, strength, quality, purity or potency of a drug product **(3)**

C. **Major:** Has a substantial potential to have an adverse effect on the identity, strength, quality, purity or potency of a drug product **(4)**

Frequency Estimation (F):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

A. **Likely:** Event may occur and/or has occurred in the past **(3)**

B. **Likely:** Event may occur and/or has occurred in the past **(3)**

C. **Unlikely:** Event not expected to occur, but theoretically possible **(2)**

Level of Detectability (D):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

A. **Readily detectable:** Will be detected **(1)**

B. **Readily detectable:** Will be detected **(1)**

C. **Readily detectable:** Will be detected (1)

Type of Data Needed to Support the Change:

A. - Validation of the new time limits (chemical and microbial)

B. - Validation of the new time limits (chemical and microbial)

C. - Validation of the new time limits (chemical and microbial)

Risk Level of Change Based on Assessment:

$$\begin{array}{c} \boxed{4} \\ \text{(S)} \end{array} \times \begin{array}{c} \boxed{3} \\ \text{(F)} \end{array} \times \begin{array}{c} \boxed{1} \\ \text{(D)} \end{array} = \begin{array}{c} \boxed{12} \\ \text{Risk Level} \end{array}$$

$$\begin{array}{c} \boxed{3} \\ \text{(S)} \end{array} \times \begin{array}{c} \boxed{3} \\ \text{(F)} \end{array} \times \begin{array}{c} \boxed{1} \\ \text{(D)} \end{array} = \begin{array}{c} \boxed{9} \\ \text{Risk Level} \end{array}$$

$$\begin{array}{c} \boxed{4} \\ \text{(S)} \end{array} \times \begin{array}{c} \boxed{2} \\ \text{(F)} \end{array} \times \begin{array}{c} \boxed{1} \\ \text{(D)} \end{array} = \begin{array}{c} \boxed{8} \\ \text{Risk Level} \end{array}$$

Overall Risk Level:

Risk Assessment #D1

Change Description in Detail:

Change of drug substance source (e.g. different facility or different manufacturer) for an aseptically produced product

Assumptions and Comments:

- The drug substance is manufactured using the same process

Possible Events:

(Negative events that could occur as a result of the change)

A. Increased bioburden from the new drug substance leads to a non-sterile drug product

B. Increased endotoxins from the new drug substance leads to increased endotoxins in the drug product

C. Chemical properties of the new drug substance lead to a chemical and/or physical stability decrease in the drug product, including an increase in the impurity levels

D. Chemical properties of the new drug substance lead to a change in impurity profile of the product

Severity of Event (S):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

A. **Major:** Has a substantial potential to have an adverse effect on the identity, strength, quality, purity or potency of a drug product **(4)**

B. **Major:** Has a substantial potential to have an adverse effect on the identity, strength, quality, purity or potency of a drug product **(4)**

C. **Moderate:** Has a moderate potential to have an adverse effect on the identity, strength, quality, purity or potency of a drug product **(3)**

D. **Moderate:** Has a moderate potential to have an adverse effect on the identity, strength, quality, purity or potency of a drug product **(3)**

Frequency Estimation (F):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

A. **Unlikely:** Not expected to occur but theoretically possible **(2)**

B. **Likely:** Event may occur or has occurred in the past **(3)**

C. **Unlikely:** Not expected to occur but theoretically possible **(2)**

D. **Unlikely:** Not expected to occur but theoretically possible **(2)**

Level of Detectability (D):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

A. **Readily detectable:** Will be detected **(1)***
* Note: Based on pre-sterilizing filter bioburden testing of bulk product

B. **Readily detectable:** Will be detected **(1)**

C. **Readily detectable:** Will be detected **(1)**

D. **May Be Detectable:** May be detected **(2)**

Type of Data Needed to Support the Change:

A. - Drug substance bioburden testing
- Pre-sterile filtered bulk product bioburden
- Product sterility testing
- Qualification of vendor and certificate of analysis

B. - Drug substance endotoxin testing
- Product endotoxin testing
- Qualification of vendor and certificate of analysis

C. - Stability data (physical and chemical stability)

D. - Product testing
- Qualification of vendor and certificate of analysis

Risk Level of Change Based on Assessment:

Event A
$$\begin{array}{c} \boxed{4} \\ (S) \end{array} \times \begin{array}{c} \boxed{2} \\ (F) \end{array} \times \begin{array}{c} \boxed{1} \\ (D) \end{array} = \begin{array}{c} \boxed{8} \\ \text{Risk Level} \end{array}$$

Event B
$$\begin{array}{c} \boxed{4} \\ (S) \end{array} \times \begin{array}{c} \boxed{3} \\ (F) \end{array} \times \begin{array}{c} \boxed{1} \\ (D) \end{array} = \begin{array}{c} \boxed{12} \\ \text{Risk Level} \end{array}$$

Event C
$$\begin{array}{c} \boxed{3} \\ (S) \end{array} \times \begin{array}{c} \boxed{2} \\ (F) \end{array} \times \begin{array}{c} \boxed{1} \\ (D) \end{array} = \begin{array}{c} \boxed{6} \\ \text{Risk Level} \end{array}$$

Event D
$$\begin{array}{c} \boxed{3} \\ (S) \end{array} \times \begin{array}{c} \boxed{2} \\ (F) \end{array} \times \begin{array}{c} \boxed{2} \\ (D) \end{array} = \begin{array}{c} \boxed{12} \\ \text{Risk Level} \end{array}$$

Overall Risk Level:

$\boxed{12}$

Risk Assessment #D2

Change Description in Detail:

Change of drug substance source (e.g. different facility or different manufacturer) for terminally sterilized product

Assumptions and Comments:

- The drug substance is manufactured using the same process

Possible Events:

(Negative events that could occur as a result of the change)

A. Increased bioburden from the new drug substance leads to a non-sterile drug product

B. Increased endotoxins from the new drug substance leads to increased endotoxins in the drug product

C. Chemical properties of the new drug substance lead to a chemical and/or physical stability decrease in the drug product, including an increase in the impurity levels

D. Chemical properties of the new drug substance lead to a change in impurity profile of the product

Severity of Event (S):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

A. **Major:** Has a substantial potential to have an adverse effect on the identity, strength, quality, purity or potency of a drug product **(4)**

B. **Major:** Has a substantial potential to have an adverse effect on the identity, strength, quality, purity or potency of a drug product **(4)**

C. **Moderate:** Has a moderate potential to have an adverse effect on the identity, strength, quality, purity or potency of a drug product **(3)**

D. **Moderate:** Has a moderate potential to have an adverse effect on the identity, strength, quality, purity or potency of a drug product **(3)**

Frequency Estimation (F):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

A. **Highly Unlikely:** The probability of the event occurring is so low that it can be assumed that the event will not occur **(1)**

B. **Likely:** Event may occur or has occurred in the past **(3)**

C. **Unlikely:** Not expected to occur but theoretically possible **(2)**

D. **Unlikely:** Not expected to occur but theoretically possible **(2)**

Level of Detectability (D):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

A. **Readily Detectable:** Will be detected **(1)***
*Based on pre-sterilizing filter bioburden testing of bulk product

B. **Readily Detectable:** Will be detected **(1)**

C. **Readily Detectable:** Will be detected **(1)**

D. **May be Detectable:** May be detected **(2)**

Type of Data Needed to Support the Change:

A. - Drug substance bioburden testing
- Pre-sterile filtered bulk product bioburden
- Product sterility testing
- Qualification of vendor and certificate of analysis

B. - Drug substance endotoxin testing
- Product endotoxin testing
- Qualification of vendor and certificate of analysis

C. - Stability data (physical and chemical stability)

D. - Product testing
- Qualification of vendor and certificate of analysis

Risk Level of Change Based on Assessment:

Event A
$$\begin{array}{c} \boxed{4} \\ (S) \end{array} \times \begin{array}{c} \boxed{1} \\ (F) \end{array} \times \begin{array}{c} \boxed{1} \\ (D) \end{array} = \begin{array}{c} \boxed{4} \\ \text{Risk Level} \end{array}$$

Event B
$$\begin{array}{c} \boxed{4} \\ (S) \end{array} \times \begin{array}{c} \boxed{3} \\ (F) \end{array} \times \begin{array}{c} \boxed{1} \\ (D) \end{array} = \begin{array}{c} \boxed{12} \\ \text{Risk Level} \end{array}$$

Event C
$$\begin{array}{c} \boxed{3} \\ (S) \end{array} \times \begin{array}{c} \boxed{2} \\ (F) \end{array} \times \begin{array}{c} \boxed{1} \\ (D) \end{array} = \begin{array}{c} \boxed{6} \\ \text{Risk Level} \end{array}$$

Event D
$$\begin{array}{c} \boxed{3} \\ (S) \end{array} \times \begin{array}{c} \boxed{2} \\ (F) \end{array} \times \begin{array}{c} \boxed{2} \\ (D) \end{array} = \begin{array}{c} \boxed{12} \\ \text{Risk Level} \end{array}$$

Overall Risk Level:

$\boxed{12}$

Risk Assessment #D3

Change Description in Detail:

Change of excipient source (e.g. different facility or different manufacturer) for an aseptically produced product.

Assumptions and Comments:

- The excipient is manufactured using the same process or a different process

Possible Events:

(Negative events that could occur as a result of the change)

A. Increased bioburden from the new excipient leads to a non-sterile drug product.

B. Increased endotoxins from the new excipient leads to increased endotoxins in the drug product

C. Chemical properties of the new excipient lead to a chemical and/or physical stability decrease of the drug product, including an increase in the impurity levels

Severity of Event (S):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

A. **Major:** Has a substantial potential to have an adverse effect on the identity, strength, quality, purity or potency of a drug product **(4)**

B. **Major:** Has a substantial potential to have an adverse effect on the identity, strength, quality, purity or potency of a drug product **(4)**

C. **Moderate:** Has a moderate potential to have an adverse effect on the identity, strength, quality, purity or potency of a drug product **(3)**

Frequency Estimation (F):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

A. **Highly Unlikely:** The probability of the event occurring is so low that it can be assumed that the event will not occur **(1)**

B. **Highly Unlikely:** The probability of the event occurring is so low that it can be assumed that the event will not occur **(1)**

C. **Highly Unlikely:** The probability of the event occurring is so low that it can be assumed that the event will not occur **(1)**

Level of Detectability (D):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

A. **Readily Detectable:** Will be detected **(1)***
*Based on pre-sterilizing filter bioburden testing of bulk product

B. **Readily Detectable:** Will be detected **(1)**

C. **Readily Detectable:** Will be detected (1)

Type of Data Needed to Support the Change:

A. - Excipient bioburden
- Pre-sterile filtered bulk product bioburden
- Product sterility testing
- Qualification of vendor and certificate of analysis

B. - Excipient endotoxin testing
- Product endotoxin testing
- Qualification of vendor and certificate of analysis

C. - Stability data (physical and chemical stability)

Risk Level of Change Based on Assessment:

Event A
$$\begin{array}{c} \boxed{4} \\ (S) \end{array} \times \begin{array}{c} \boxed{1} \\ (F) \end{array} \times \begin{array}{c} \boxed{1} \\ (D) \end{array} = \begin{array}{c} \boxed{4} \\ \text{Risk Level} \end{array}$$

Event B
$$\begin{array}{c} \boxed{4} \\ (S) \end{array} \times \begin{array}{c} \boxed{1} \\ (F) \end{array} \times \begin{array}{c} \boxed{1} \\ (D) \end{array} = \begin{array}{c} \boxed{4} \\ \text{Risk Level} \end{array}$$

Event C
$$\begin{array}{c} \boxed{3} \\ (S) \end{array} \times \begin{array}{c} \boxed{1} \\ (F) \end{array} \times \begin{array}{c} \boxed{1} \\ (D) \end{array} = \begin{array}{c} \boxed{3} \\ \text{Risk Level} \end{array}$$

Overall Risk Level:

$\boxed{4}$

Risk Assessment #D4

Change Description in Detail:

Change of excipient source (e.g. different facility or different manufacturer) for a terminally sterilized product.

Assumptions and Comments:

- The excipient is manufactured using the same process or a different process

Possible Events:

(Negative events that could occur as a result of the change)

A. Increased bioburden from the new excipient leads to a non-sterile drug product

B. Increased endotoxins from the new excipient leads to increased endotoxins in the drug product

C. Chemical properties of the new excipient lead to a chemical and/or physical stability decrease of the drug product, including an increase in the impurity levels

Severity of Event (S):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

A. **Major:** Has a substantial potential to have an adverse effect on the identity, strength, quality, purity or potency of a drug product **(4)**

B. **Major:** Has a substantial potential to have an adverse effect on the identity, strength, quality, purity or potency of a drug product **(4)**

C. **Moderate:** Has a moderate potential to have an adverse effect on the identity, strength, quality, purity or potency of a drug product **(3)**

Frequency Estimation (F):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

A. **Highly Unlikely:** The probability of the event occurring is so low that it can be assumed that the event will not occur **(1)**

B. **Highly Unlikely:** The probability of the event occurring is so low that it can be assumed that the event will not occur **(1)**

C. **Highly Unlikely:** The probability of the event occurring is so low that it can be assumed that the event will not occur **(1)**

Level of Detectability (D):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

A. **Readily Detectable:** Will be detected **(1)**

B. **Readily Detectable:** Will be detected **(1)**

C. **Readily Detectable:** Will be detected **(1)**

Type of Data Needed to Support the Change:

- A. - Excipient bioburden
- Pre-sterile filtered bulk product bioburden
- Product sterility testing
- Qualification of vendor and certificate of analysis

- B. - Excipient endotoxin testing
- Product endotoxin testing
- Qualification of vendor and certificate of analysis

- C. - Stability data (physical and chemical stability)

Risk Level of Change Based on Assessment:

Event A

$$\begin{array}{c} \boxed{4} \\ (S) \end{array} \times \begin{array}{c} \boxed{1} \\ (F) \end{array} \times \begin{array}{c} \boxed{1} \\ (D) \end{array} = \begin{array}{c} \boxed{4} \\ \text{Risk Level} \end{array}$$

Event B

$$\begin{array}{c} \boxed{4} \\ (S) \end{array} \times \begin{array}{c} \boxed{1} \\ (F) \end{array} \times \begin{array}{c} \boxed{1} \\ (D) \end{array} = \begin{array}{c} \boxed{4} \\ \text{Risk Level} \end{array}$$

Event C

$$\begin{array}{c} \boxed{3} \\ (S) \end{array} \times \begin{array}{c} \boxed{1} \\ (F) \end{array} \times \begin{array}{c} \boxed{1} \\ (D) \end{array} = \begin{array}{c} \boxed{3} \\ \text{Risk Level} \end{array}$$

Overall Risk Level:

$\boxed{4}$

Risk Assessment #D5

Change Description in Detail:

Change in composition of container materials for solutions, suspensions, emulsions and other dispersed systems for injectables administered intravenously

Assumptions and Comments:

- The size and shape of the container has not changed and the closure has not changed
- The change is from glass to glass (can include change from molded to tubular and vice versa) or plastic to plastic

Possible Events:

(Negative events that could occur as a result of the change)

A. Particulates increase in drug product

B. Leachables increase or different profile of leachables in drug product

C. Chemical and/or physical stability profile of drug product decreases

D. Lack of container closure integrity leads to the production of non-sterile drug product

Severity of Event (S):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

A **Moderate:** Has a moderate potential to have an adverse effect on the identity, strength, quality, purity or potency of a drug product **(3)**

B. **Moderate:** Has a moderate potential to have an adverse effect on the identity, strength, quality, purity or potency of a drug product **(3)**

C **Moderate:** Has a moderate potential to have an adverse effect on the identity, strength, quality, purity or potency of a drug product **(3)**

D. **Major:** Has a substantial potential to have an adverse effect on the identity, strength, quality, purity or potency of a drug product **(4)**

Frequency Estimation (F):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

A. **Likely:** Event may occur and/or has occurred in the past **(3)**

B. **Likely:** Event may occur and/or has occurred in the past **(3)**

C. **Likely:** Event may occur and/or has occurred in the past **(3)**

D. **Unlikely:** Event not expected to occur, but theoretically possible **(2)**

Level of Detectability (D):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

- A. **Readily Detectable:** Will be detected (1)
- B. **Readily Detectable:** Will be detected (1)
- C. **Readily Detectable:** Will be detected (1)
- D. **Readily Detectable:** Will be detected (1)

Type of Data Needed to Support the Change:

- A. - Qualify container composition for use with drug product, i.e., leachables testing, particulates, stability testing
- B. - Qualify container composition for use with drug product, i.e. leachables testing, particulates, stability testing
- C. - Qualify container composition for use with drug product, i.e. leachables testing, particulates, stability testing
- D. - Container closure integrity testing

Risk Level of Change Based on Assessment:

Event A

$$\begin{matrix} \boxed{3} \\ (S) \end{matrix} \times \begin{matrix} \boxed{3} \\ (F) \end{matrix} \times \begin{matrix} \boxed{1} \\ (D) \end{matrix} = \begin{matrix} \boxed{9} \\ \text{Risk Level} \end{matrix}$$

Event B

$$\begin{matrix} \boxed{3} \\ (S) \end{matrix} \times \begin{matrix} \boxed{3} \\ (F) \end{matrix} \times \begin{matrix} \boxed{1} \\ (D) \end{matrix} = \begin{matrix} \boxed{9} \\ \text{Risk Level} \end{matrix}$$

Event C

$$\begin{matrix} \boxed{3} \\ (S) \end{matrix} \times \begin{matrix} \boxed{3} \\ (F) \end{matrix} \times \begin{matrix} \boxed{1} \\ (D) \end{matrix} = \begin{matrix} \boxed{9} \\ \text{Risk Level} \end{matrix}$$

Event D

$$\begin{matrix} \boxed{4} \\ (S) \end{matrix} \times \begin{matrix} \boxed{2} \\ (F) \end{matrix} \times \begin{matrix} \boxed{1} \\ (D) \end{matrix} = \begin{matrix} \boxed{8} \\ \text{Risk Level} \end{matrix}$$

Overall Risk Level:

$\boxed{9}$

Risk Assessment #D6

Change Description in Detail:

Change in composition of container materials for solutions, suspensions, emulsions and other dispersed systems for injectables administered non-intravenously

Assumptions and Comments:

- The size and shape of the container has not changed and the closure has not changed
- The change is from glass to glass (can include change from molded to tubular and vice versa) or plastic to plastic

Possible Events:

(Negative events that could occur as a result of the change)

A. Particulates increase in drug product

B. Leachables increase or different profile of leachables in drug product

C. Chemical and/or physical stability profile of drug product decreases

D. Lack of container closure integrity leads to the production of a non-sterile drug product

Severity of Event (S):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

A **Minor:** Has minimal potential to have an adverse effect on the identity, strength, quality, purity or potency of a drug product **(2)**

B. **Moderate:** Has a moderate potential to have an adverse effect on the identity, strength, quality, purity or potency of a drug product **(3)**

C **Moderate:** Has a moderate potential to have an adverse effect on the identity, strength, quality, purity or potency of a drug product **(3)**

D. **Major:** Has a substantial potential to have an adverse effect on the identity, strength, quality, purity or potency of a drug product **(4)**

Frequency Estimation (F):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

A. **Likely:** Event may occur and/or has occurred in the past **(3)**

B. **Likely:** Event may occur and/or has occurred in the past **(3)**

C. **Likely:** Event may occur and/or has occurred in the past **(3)**

D. **Unlikely:** Event not expected to occur, but theoretically possible **(2)**

Level of Detectability (D):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

- A. **Readily Detectable:** Will be detected (1)
- B. **Readily Detectable:** Will be detected (1)
- C. **Readily Detectable:** Will be detected (1)
- D. **Readily Detectable:** Will be detected (1)

Type of Data Needed to Support the Change:

- A. - Qualify container composition for use with drug product, i.e. leachables testing, particulates, stability testing
- B. - Qualify container composition for use with drug product, i.e. leachables testing, particulates, stability testing
- C. - Qualify container composition for use with drug product, i.e. leachables testing, particulates, stability testing
- D. - Container closure integrity testing

Risk Level of Change Based on Assessment:

Event A

$$\begin{matrix} \boxed{2} \\ (S) \end{matrix} \times \begin{matrix} \boxed{3} \\ (F) \end{matrix} \times \begin{matrix} \boxed{1} \\ (D) \end{matrix} = \begin{matrix} \boxed{6} \\ \text{Risk Level} \end{matrix}$$

Event B

$$\begin{matrix} \boxed{3} \\ (S) \end{matrix} \times \begin{matrix} \boxed{3} \\ (F) \end{matrix} \times \begin{matrix} \boxed{1} \\ (D) \end{matrix} = \begin{matrix} \boxed{9} \\ \text{Risk Level} \end{matrix}$$

Event C

$$\begin{matrix} \boxed{3} \\ (S) \end{matrix} \times \begin{matrix} \boxed{3} \\ (F) \end{matrix} \times \begin{matrix} \boxed{1} \\ (D) \end{matrix} = \begin{matrix} \boxed{9} \\ \text{Risk Level} \end{matrix}$$

Event D

$$\begin{matrix} \boxed{4} \\ (S) \end{matrix} \times \begin{matrix} \boxed{2} \\ (F) \end{matrix} \times \begin{matrix} \boxed{1} \\ (D) \end{matrix} = \begin{matrix} \boxed{8} \\ \text{Risk Level} \end{matrix}$$

Overall Risk Level:

$\boxed{9}$

Risk Assessment #D7

Change Description in Detail:

Change in composition of container materials for powder fill, lyophilized, and other solids for injectables administered intravenously after reconstitution

Assumptions and Comments:

- The size and shape of the container has not changed and the closure has not changed
- The change is from glass to glass (can include change from molded to tubular and vice versa) or plastic to plastic

Possible Events:

(Negative events that could occur as a result of the change)

A. Particulates increase in drug product

B. Leachables increase or different profile of leachables in drug product

C. Chemical and/or physical stability profile of drug product decreases

D. Lack of container closure integrity leads to the production of non-sterile drug product

Severity of Event (S):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

A. **Moderate:** Has a moderate potential to have an adverse effect on the identity, strength, quality, purity or potency of a drug product **(3)**

B. **Moderate:** Has a moderate potential to have an adverse effect on the identity, strength, quality, purity or potency of a drug product **(3)**

C. **Moderate:** Has a moderate potential to have an adverse effect on the identity, strength, quality, purity or potency of a drug product **(3)**

D. **Major:** Has a substantial potential to have an adverse effect on the identity, strength, quality, purity or potency of a drug product **(4)**

Frequency Estimation (F):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

A. **Unlikely:** Event not expected to occur, but theoretically possible **(2)**

B. **Unlikely:** Event not expected to occur, but theoretically possible **(2)**

C. **Unlikely:** Event not expected to occur, but theoretically possible **(2)**

D. **Unlikely:** Event not expected to occur, but theoretically possible **(2)**

Level of Detectability (D):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

A. **Readily Detectable:** Will be detected (1)

B. **Readily Detectable:** Will be detected (1)

C. **Readily Detectable:** Will be detected (1)

D. **Readily Detectable:** Will be detected (1)

Type of Data Needed to Support the Change:

A. - Qualify container composition for use with drug product, i.e. leachables testing, particulates, stability testing

B. - Qualify container composition for use with drug product, i.e. leachables testing, particulates, stability testing

C. - Qualify container composition for use with drug product, i.e. leachables testing, particulates, stability testing

D. - Container closure integrity testing

Risk Level of Change Based on Assessment:

Event A

$$\begin{array}{c} \boxed{3} \\ (S) \end{array} \times \begin{array}{c} \boxed{2} \\ (F) \end{array} \times \begin{array}{c} \boxed{1} \\ (D) \end{array} = \begin{array}{c} \boxed{6} \\ \text{Risk Level} \end{array}$$

Event B

$$\begin{array}{c} \boxed{3} \\ (S) \end{array} \times \begin{array}{c} \boxed{2} \\ (F) \end{array} \times \begin{array}{c} \boxed{1} \\ (D) \end{array} = \begin{array}{c} \boxed{6} \\ \text{Risk Level} \end{array}$$

Event C

$$\begin{array}{c} \boxed{3} \\ (S) \end{array} \times \begin{array}{c} \boxed{2} \\ (F) \end{array} \times \begin{array}{c} \boxed{1} \\ (D) \end{array} = \begin{array}{c} \boxed{6} \\ \text{Risk Level} \end{array}$$

Event D

$$\begin{array}{c} \boxed{4} \\ (S) \end{array} \times \begin{array}{c} \boxed{2} \\ (F) \end{array} \times \begin{array}{c} \boxed{1} \\ (D) \end{array} = \begin{array}{c} \boxed{8} \\ \text{Risk Level} \end{array}$$

Overall Risk Level:

$$\boxed{8}$$

Risk Assessment #D8

Change Description in Detail:

Change in composition of container materials for powder fill, lyophilized, and other solids for injectables administered non-intravenously after reconstitution

Assumptions and Comments:

- The size and shape of the container has not changed and the closure has not changed
- The change is from glass to glass (can include change from molded to tubular and vice versa) or plastic to plastic

Possible Events:

(Negative events that could occur as a result of the change)

A. Particulates increase in drug product

B. Leachables increase or different profile of leachables in drug product

C. Chemical and/or physical stability profile of drug product decreases

D. Lack of container closure integrity leads to the production of non-sterile drug product

Severity of Event (S):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

A. **Minor:** Has minimal potential to have an adverse effect on the identity, strength, quality, purity or potency of a drug product **(2)**

B. **Moderate:** Has a moderate potential to have an adverse effect on the identity, strength, quality, purity or potency of a drug product **(3)**

C. **Moderate:** Has a moderate potential to have an adverse effect on the identity, strength, quality, purity or potency of a drug product **(3)**

D. **Major:** Has a substantial potential to have an adverse effect on the identity, strength, quality, purity or potency of a drug product **(4)**

Frequency Estimation (F):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

A. **Unlikely:** Event not expected to occur, but theoretically possible **(2)**

B. **Unlikely:** Event not expected to occur, but theoretically possible **(2)**

C. **Unlikely:** Event not expected to occur, but theoretically possible **(2)**

D. **Unlikely:** Event not expected to occur, but theoretically possible **(2)**

Level of Detectability (D):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

A. **Readily Detectable:** Will be detected (1)

B. **Readily Detectable:** Will be detected (1)

C. **Readily Detectable:** Will be detected (1)

D. **Readily Detectable:** Will be detected (1)

Type of Data Needed to Support the Change:

A. - Qualify container composition for use with drug product, i.e. leachables testing, particulates, stability testing

B. - Qualify container composition for use with drug product, i.e. leachables testing, particulates, stability testing

C. - Qualify container composition for use with drug product, i.e. leachables testing, particulates, stability testing

D. - Container closure integrity testing

Risk Level of Change Based on Assessment:

Event A

$$\frac{2}{(S)} \times \frac{2}{(F)} \times \frac{1}{(D)} = \frac{4}{\text{Risk Level}}$$

Event B

$$\frac{3}{(S)} \times \frac{2}{(F)} \times \frac{1}{(D)} = \frac{6}{\text{Risk Level}}$$

Event C

$$\frac{3}{(S)} \times \frac{2}{(F)} \times \frac{1}{(D)} = \frac{6}{\text{Risk Level}}$$

Event D

$$\frac{4}{(S)} \times \frac{2}{(F)} \times \frac{1}{(D)} = \frac{8}{\text{Risk Level}}$$

Overall Risk Level:

8

Risk Assessment #D9

Change Description in Detail:

Change in size and/or shape of container for an aseptically produced product

Assumptions and Comments:

- No change in container composition
- No change in closure (size or composition)
- No change in fill volume

Possible Events:

(Negative events that could occur as a result of the change)

A. Chemical and/or physical stability of product decreases

B. Change in the container impacts the manufacturing performance and leads to the production of non-sterile drug product

C. Lack of container closure integrity leads to the production of non-sterile drug product

Severity of Event (S):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

A **Moderate:** Has a moderate potential to have an adverse effect on the identity, strength, quality, purity or potency of a drug product **(3)**

B **Major:** Has a substantial potential to have an adverse effect on the identity, strength, quality, purity or potency of a drug product **(4)**

C **Major:** Has a substantial potential to have an adverse effect on the identity, strength, quality, purity or potency of a drug product **(4)**

Frequency Estimation (F):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

A. **Unlikely:** Event not expected to occur, but theoretically possible **(2)**

B. **Likely:** Event may occur and/or has occurred in the past **(3)**

C. **Unlikely:** Event not expected to occur, but theoretically possible **(2)**

Level of Detectability (D):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

A. **Readily Detectable:** Will be detected **(1)**

B. **Readily Detectable:** Will be detected **(1)**

C. **Readily Detectable:** Will be detected **(1)**

Type of Data Needed to Support the Change:

A. - Qualify container size and shape, i.e. stability testing, headspace analysis, etc
- For lyophilized products process validation

B. - Validation of sterilization process using new container with media fills
- Machineability studies

C. - Container closure integrity testing

Risk Level of Change Based on Assessment:

Event A

$$\begin{array}{c} \boxed{3} \\ (S) \end{array} \times \begin{array}{c} \boxed{2} \\ (F) \end{array} \times \begin{array}{c} \boxed{1} \\ (D) \end{array} = \begin{array}{c} \boxed{6} \\ \text{Risk Level} \end{array}$$

Event B

$$\begin{array}{c} \boxed{4} \\ (S) \end{array} \times \begin{array}{c} \boxed{3} \\ (F) \end{array} \times \begin{array}{c} \boxed{1} \\ (D) \end{array} = \begin{array}{c} \boxed{12} \\ \text{Risk Level} \end{array}$$

Event C

$$\begin{array}{c} \boxed{4} \\ (S) \end{array} \times \begin{array}{c} \boxed{2} \\ (F) \end{array} \times \begin{array}{c} \boxed{1} \\ (D) \end{array} = \begin{array}{c} \boxed{8} \\ \text{Risk Level} \end{array}$$

Overall Risk Level:

$$\boxed{12}$$

Risk Assessment #D10

Change Description in Detail:

Change in size and/or shape of container for terminally sterilized sterile product

Assumptions and Comments:

- No change in container composition
- No change in closure size
- No change in fill volume

Possible Events:

(Negative events that could occur as a result of the change)

A. Chemical and/or physical stability of product decreases

B. Change in the container impacts the sterilizer performance and leads to the production of non-sterile drug product

C. Lack of container closure integrity leads to the production of non-sterile drug product

Severity of Event (S):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

A. **Moderate:** Has a moderate potential to have an adverse effect on the identity, strength, quality, purity or potency of a drug product **(3)**

B. **Major:** Has a substantial potential to have an adverse effect on the identity, strength, quality, purity or potency of a drug product **(4)**

C. **Major:** Has a substantial potential to have an adverse effect on the identity, strength, quality, purity or potency of a drug product **(4)**

Frequency Estimation (F):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

A. **Unlikely:** Event not expected to occur, but theoretically possible **(2)**

B. **Highly Unlikely:** The probability of the event occurring is so low it can be assumed that the event will not occur **(1)**

C. **Unlikely:** Event not expected to occur, but theoretically possible **(2)**

Level of Detectability (D):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

A. **Readily Detectable:** Will be detected **(1)**

B. **Readily Detectable:** Will be detected **(1)**

C. **Readily Detectable:** Will be detected **(1)**

Type of Data Needed to Support the Change:

A. - Qualify container size and shape, i.e. stability testing, headspace analysis, etc

B. - Validation of sterilization process using new container with media fills
- Machineability studies

C. - Container closure integrity testing

Risk Level of Change Based on Assessment:

Event A

$$\begin{array}{c} \boxed{3} \\ (S) \end{array} \times \begin{array}{c} \boxed{2} \\ (F) \end{array} \times \begin{array}{c} \boxed{1} \\ (D) \end{array} = \begin{array}{c} \boxed{6} \\ \text{Risk Level} \end{array}$$

Event B

$$\begin{array}{c} \boxed{4} \\ (S) \end{array} \times \begin{array}{c} \boxed{1} \\ (F) \end{array} \times \begin{array}{c} \boxed{1} \\ (D) \end{array} = \begin{array}{c} \boxed{4} \\ \text{Risk Level} \end{array}$$

Event C

$$\begin{array}{c} \boxed{4} \\ (S) \end{array} \times \begin{array}{c} \boxed{2} \\ (F) \end{array} \times \begin{array}{c} \boxed{1} \\ (D) \end{array} = \begin{array}{c} \boxed{8} \\ \text{Risk Level} \end{array}$$

Overall Risk Level:

$$\boxed{8}$$

Risk Assessments #D11

Change Description in Detail:

Change in composition of closure materials for solutions, suspensions, emulsions and other dispersed systems for injectables administered intravenously

Assumptions and Comments:

- The size and shape of the closure has not changed and the container has not changed
- The change involves closure formulation and/or coating of the closure

Possible Events:

(Negative events that could occur as a result of the change)

A. Particulates increase in drug product

B. Leachables increase or different profile of leachables in drug product

C. Chemical and/or physical stability profile of drug product decreases

D. Lack of container closure integrity leads to the production of non-sterile products

Severity of Event (S):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

A. **Moderate:** Has a moderate potential to have an adverse effect on the identity, strength, quality, purity or potency of a drug product **(3)**

B. **Moderate:** Has a moderate potential to have an adverse effect on the identity, strength, quality, purity or potency of a drug product **(3)**

C. **Moderate:** Has a moderate potential to have an adverse effect on the identity, strength, quality, purity or potency of a drug product **(3)**

D. **Major:** Has a substantial potential to have an adverse effect on the identity, strength, quality, purity or potency of a drug product **(4)**

Frequency Estimation (F):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

A. **Likely:** Event may occur and/or has occurred in the past **(3)**

B. **Likely:** Event may occur and/or has occurred in the past **(3)**

C. **Likely:** Event may occur and/or has occurred in the past **(3)**

D. **Unlikely:** Event not expected to occur, but theoretically possible **(2)**

Level of Detectability (D):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

A. **Readily Detectable:** Will be detected (1)

B. **Readily Detectable:** Will be detected (1)

C. **Readily Detectable:** Will be detected (1)

D. **Readily Detectable:** Will be detected (1)

Type of Data Needed to Support the Change:

A. - Qualify closure composition for use with drug product, i.e. leachables testing, particulates, stability testing

B. - Qualify closure composition for use with drug product, i.e. leachables testing, particulates, stability testing

C. - Qualify closure composition for use with drug product, i.e. leachables testing, particulates, stability testing

D. - Container closure integrity testing

Risk Level of Change Based on Assessment:

Event A

$$\begin{array}{c} \boxed{3} \\ (S) \end{array} \times \begin{array}{c} \boxed{3} \\ (F) \end{array} \times \begin{array}{c} \boxed{1} \\ (D) \end{array} = \begin{array}{c} \boxed{9} \\ \text{Risk Level} \end{array}$$

Event B

$$\begin{array}{c} \boxed{3} \\ (S) \end{array} \times \begin{array}{c} \boxed{3} \\ (F) \end{array} \times \begin{array}{c} \boxed{1} \\ (D) \end{array} = \begin{array}{c} \boxed{9} \\ \text{Risk Level} \end{array}$$

Event C

$$\begin{array}{c} \boxed{3} \\ (S) \end{array} \times \begin{array}{c} \boxed{3} \\ (F) \end{array} \times \begin{array}{c} \boxed{1} \\ (D) \end{array} = \begin{array}{c} \boxed{9} \\ \text{Risk Level} \end{array}$$

Event D

$$\begin{array}{c} \boxed{4} \\ (S) \end{array} \times \begin{array}{c} \boxed{2} \\ (F) \end{array} \times \begin{array}{c} \boxed{1} \\ (D) \end{array} = \begin{array}{c} \boxed{8} \\ \text{Risk Level} \end{array}$$

Overall Risk Level:

$\boxed{9}$

Risk Assessment #D12

Change Description in Detail:

Change in composition of closure materials for solutions, suspensions, emulsions and other dispersed systems for injectables administered via route other than intravenously

Assumptions and Comments:

- The size and shape of the closure has not changed and the container has not changed
- The change involves closure formulation and/or coating of the closure

Possible Events:

(Negative events that could occur as a result of the change)

A. Particulates increase in drug product

B. Leachables increase or different profile of leachables in drug product

C. Chemical and/or physical stability profile of drug product decreases

D. Lack of container closure integrity leads to the production of non-sterile products

Severity of Event (S):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

A. **Minor:** Has minimal potential to have an adverse effect on the identity, strength, quality, purity or potency of a drug product **(2)**

B. **Moderate:** Has a moderate potential to have an adverse effect on the identity, strength, quality, purity or potency of a drug product **(3)**

C. **Moderate:** Has a moderate potential to have an adverse effect on the identity, strength, quality, purity or potency of a drug product **(3)**

D. **Major:** Has a substantial potential to have an adverse effect on the identity, strength, quality, purity or potency of a drug product **(4)**

Frequency Estimation (F):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

A. **Likely:** Event may occur and/or has occurred in the past **(3)**

B. **Likely:** Event may occur and/or has occurred in the past **(3)**

C. **Likely:** Event may occur and/or has occurred in the past **(3)**

D. **Unlikely:** Event not expected to occur, but theoretically possible **(2)**

Level of Detectability (D):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

A. **Readily Detectable:** Will be detected **(1)**

B. **Readily Detectable:** Will be detected (1)

C. **Readily Detectable:** Will be detected (1)

D. **Readily Detectable:** Will be detected (1)

Type of Data Needed to Support the Change:

A. - Qualify closure composition for use with drug product, i.e. leachables testing, particulates, stability testing

B. - Qualify closure composition for use with drug product, i.e. leachables testing, particulates, stability testing

C. - Qualify closure composition for use with drug product, i.e. leachables testing, particulates, stability testing

D. - Container closure integrity testing

Risk Level of Change Based on Assessment:

Event A

$$\begin{array}{c} \boxed{2} \\ (S) \end{array} \times \begin{array}{c} \boxed{3} \\ (F) \end{array} \times \begin{array}{c} \boxed{1} \\ (D) \end{array} = \begin{array}{c} \boxed{6} \\ \text{Risk Level} \end{array}$$

Event B

$$\begin{array}{c} \boxed{3} \\ (S) \end{array} \times \begin{array}{c} \boxed{3} \\ (F) \end{array} \times \begin{array}{c} \boxed{1} \\ (D) \end{array} = \begin{array}{c} \boxed{9} \\ \text{Risk Level} \end{array}$$

Event C

$$\begin{array}{c} \boxed{3} \\ (S) \end{array} \times \begin{array}{c} \boxed{3} \\ (F) \end{array} \times \begin{array}{c} \boxed{1} \\ (D) \end{array} = \begin{array}{c} \boxed{9} \\ \text{Risk Level} \end{array}$$

Event D

$$\begin{array}{c} \boxed{4} \\ (S) \end{array} \times \begin{array}{c} \boxed{2} \\ (F) \end{array} \times \begin{array}{c} \boxed{1} \\ (D) \end{array} = \begin{array}{c} \boxed{8} \\ \text{Risk Level} \end{array}$$

Overall Risk Level:

$$\boxed{9}$$

Risk Assessment #D13

Change Description in Detail:

Change in composition of closure materials for powder fill, lyophilized, and other solids for injectables administered intravenously after reconstitution

Assumptions and Comments:

- The size and shape of the closure has not changed and the container has not changed
- The change involves closure formulation and/or coating of the closure

Possible Events:

(Negative events that could occur as a result of the change)

A. Particulates increase in drug product

B. Leachables increase or different profile of leachables in drug product

C. Chemical and/or physical stability profile of drug product decreases

D. Lack of container closure integrity leads to the production of non-sterile products

Severity of Event (S):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

A. **Moderate:** Has a moderate potential to have an adverse effect on the identity, strength, quality, purity or potency of a drug product **(3)**

B. **Moderate:** Has a moderate potential to have an adverse effect on the identity, strength, quality, purity or potency of a drug product **(3)**

C. **Moderate:** Has a moderate potential to have an adverse effect on the identity, strength, quality, purity or potency of a drug product **(3)**

D. **Major:** Has a substantial potential to have an adverse effect on the identity, strength, quality, purity or potency of a drug product **(4)**

Frequency Estimation (F):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

A. **Unlikely:** Event not expected to occur, but theoretically possible **(2)**

B. **Unlikely:** Event not expected to occur, but theoretically possible **(2)**

C. **Unlikely:** Event not expected to occur, but theoretically possible **(2)**

D. **Unlikely:** Event not expected to occur, but theoretically possible **(2)**

Level of Detectability (D):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

A. **Readily Detectable:** Will be detected **(1)**

B. **Readily Detectable:** Will be detected (1)

C. **Readily Detectable:** Will be detected (1)

D. **Readily Detectable:** Will be detected (1)

Type of Data Needed to Support the Change:

A. - Qualify closure composition for use with drug product, i.e. leachables testing, particulates, stability testing

B. - Qualify closure composition for use with drug product, i.e. leachables testing, particulates, stability testing

C. - Qualify closure composition for use with drug product, i.e. leachables testing, particulates, stability testing

D. - Container closure integrity testing

Risk Level of Change Based on Assessment:

Event A

$$\begin{array}{c} \boxed{3} \\ (S) \end{array} \times \begin{array}{c} \boxed{2} \\ (F) \end{array} \times \begin{array}{c} \boxed{1} \\ (D) \end{array} = \begin{array}{c} \boxed{6} \\ \text{Risk Level} \end{array}$$

Event B

$$\begin{array}{c} \boxed{3} \\ (S) \end{array} \times \begin{array}{c} \boxed{2} \\ (F) \end{array} \times \begin{array}{c} \boxed{1} \\ (D) \end{array} = \begin{array}{c} \boxed{6} \\ \text{Risk Level} \end{array}$$

Event C

$$\begin{array}{c} \boxed{3} \\ (S) \end{array} \times \begin{array}{c} \boxed{2} \\ (F) \end{array} \times \begin{array}{c} \boxed{1} \\ (D) \end{array} = \begin{array}{c} \boxed{6} \\ \text{Risk Level} \end{array}$$

Event D

$$\begin{array}{c} \boxed{4} \\ (S) \end{array} \times \begin{array}{c} \boxed{2} \\ (F) \end{array} \times \begin{array}{c} \boxed{1} \\ (D) \end{array} = \begin{array}{c} \boxed{8} \\ \text{Risk Level} \end{array}$$

Overall Risk Level:

$\boxed{8}$

Risk Assessment #D14

Change Description in Detail:

Change in composition of closure materials for powder fill, lyophilized, and other solids for injectables administered via route other than intravenously after reconstitution

Assumptions and Comments:

- The size and shape of the closure has not changed and the container has not changed.
- The change involves closure formulation and/or coating of the closure

Possible Events:

(Negative events that could occur as a result of the change)

A. Particulates increase in drug product

B. Leachables increase or different profile of leachables in drug product

C. Chemical and/or physical stability profile of drug product decreases

D. Lack of container closure integrity leads to the production of non-sterile products

Severity of Event (S):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

A. **Minor:** Has minimal potential to have an adverse effect on the identity, strength, quality, purity or potency of a drug product **(2)**

B. **Moderate:** Has a moderate potential to have an adverse effect on the identity, strength, quality, purity or potency of a drug product **(3)**

C. **Moderate:** Has a moderate potential to have an adverse effect on the identity, strength, quality, purity or potency of a drug product **(3)**

D. **Major:** Has a substantial potential to have an adverse effect on the identity, strength, quality, purity or potency of a drug product **(4)**

Frequency Estimation (F):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

A. **Unlikely:** Event not expected to occur, but theoretically possible **(2)**

B. **Unlikely:** Event not expected to occur, but theoretically possible **(2)**

C. **Unlikely:** Event not expected to occur, but theoretically possible **(2)**

D. **Unlikely:** Event not expected to occur, but theoretically possible **(2)**

Level of Detectability (D):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

A. **Readily Detectable:** Will be detected (1)

B. **Readily Detectable:** Will be detected (1)

C. **Readily Detectable:** Will be detected (1)

D. **Readily Detectable:** Will be detected (1)

Type of Data Needed to Support the Change:

A. - Qualify closure composition for use with drug product, i.e. leachables testing, particulates, stability testing

B. - Qualify closure composition for use with drug product, i.e. leachables testing, particulates, stability testing

C. - Qualify closure composition for use with drug product, i.e. leachables testing, particulates, stability testing

D. - Container closure integrity testing

Risk Level of Change Based on Assessment:

Event A

$$\begin{array}{c} \boxed{2} \\ (S) \end{array} \times \begin{array}{c} \boxed{2} \\ (F) \end{array} \times \begin{array}{c} \boxed{1} \\ (D) \end{array} = \begin{array}{c} \boxed{4} \\ \text{Risk Level} \end{array}$$

Event B

$$\begin{array}{c} \boxed{3} \\ (S) \end{array} \times \begin{array}{c} \boxed{2} \\ (F) \end{array} \times \begin{array}{c} \boxed{1} \\ (D) \end{array} = \begin{array}{c} \boxed{6} \\ \text{Risk Level} \end{array}$$

Event C

$$\begin{array}{c} \boxed{3} \\ (S) \end{array} \times \begin{array}{c} \boxed{2} \\ (F) \end{array} \times \begin{array}{c} \boxed{1} \\ (D) \end{array} = \begin{array}{c} \boxed{6} \\ \text{Risk Level} \end{array}$$

Event D

$$\begin{array}{c} \boxed{4} \\ (S) \end{array} \times \begin{array}{c} \boxed{2} \\ (F) \end{array} \times \begin{array}{c} \boxed{1} \\ (D) \end{array} = \begin{array}{c} \boxed{8} \\ \text{Risk Level} \end{array}$$

Overall Risk Level:

$\boxed{8}$

Risk Assessments #D15

Change Description in Detail:

Change of container source, e.g. different facility or different manufacturer

Assumptions and Comments:

- Container is same type, composition, size and shape. Only change is the source

Possible Events:

(Negative events that could occur as a result of the change)

A. Particulates increase in drug product

B. Physical dimension variability increase leads to the production of non-sterile drug products

Severity of Event (S):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

A. **Moderate:** Has a moderate potential to have an adverse effect on the identity, strength, quality, purity or potency of a drug product **(3)**

B. **Major:** Has a substantial potential to have an adverse effect on the identity, strength, quality, purity or potency of a drug product **(4)**

Frequency Estimation (F):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

A. **Highly Unlikely:** The probability of the event occurring is so low it can be assumed that the event will not occur **(1)**

B. **Highly Unlikely:** The probability of the event occurring is so low it can be assumed that the event will not occur **(1)**

Level of Detectability (D):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

A. **Readily Detectable:** Will be detected **(1)**

B. **Readily Detectable:** Will be detected **(1)**

Type of Data Needed to Support the Change:

A. - Qualification of vendor, incoming inspection, vendor certificate of analysis

B. - Incoming analysis, specifications, vendor certificate of analysis, vendor qualification

Risk Level of Change Based on Assessment:

Event A

$$\begin{array}{c} \boxed{3} \\ (S) \end{array} \times \begin{array}{c} \boxed{1} \\ (F) \end{array} \times \begin{array}{c} \boxed{1} \\ (D) \end{array} = \begin{array}{c} \boxed{3} \\ \text{Risk Level} \end{array}$$

Event B

$$\begin{array}{c} \boxed{4} \\ (S) \end{array} \times \begin{array}{c} \boxed{1} \\ (F) \end{array} \times \begin{array}{c} \boxed{1} \\ (D) \end{array} = \begin{array}{c} \boxed{4} \\ \text{Risk Level} \end{array}$$

Overall Risk Level:

$$\boxed{4}$$

Risk Assessments #D16

Change Description in Detail:

Change of closure source, e.g. different facility or different manufacturer

Assumptions and Comments:

- Closure is same type, composition, size and shape. Only change is the source

Possible Events:

(Negative events that could occur as a result of the change)

A. Particulates increase in drug product

B. Physical dimension variability increase leads to the production of non-sterile drug products

Severity of Event (S):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

A. **Moderate:** Has a moderate potential to have an adverse effect on the identity, strength, quality, purity or potency of a drug product **(3)**

B. **Major:** Has a substantial potential to have an adverse effect on the identity, strength, quality, purity or potency of a drug product **(4)**

Frequency Estimation (F):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

A. **Highly Unlikely:** The probability of the event occurring is so low it can be assumed that the event will not occur **(1)**

B. **Highly Unlikely:** The probability of the event occurring is so low it can be assumed that the event will not occur **(1)**

Level of Detectability (D):

(Complete for each event identified in the Possible Event section above. A risk assessment value should be identified for each event.)

A. **Readily Detectable:** Will be detected **(1)**

B. **Readily Detectable:** Will be detected **(1)**

Type of Data Needed to Support the Change:

A. - Qualification of vendor, incoming inspection, vendor certificate of analysis

B. - Incoming analysis, specifications, vendor certificate of analysis, vendor qualification

Risk Level of Change Based on Assessment:

Event A

$$\begin{array}{c} \boxed{3} \\ (S) \end{array} \times \begin{array}{c} \boxed{1} \\ (F) \end{array} \times \begin{array}{c} \boxed{1} \\ (D) \end{array} = \begin{array}{c} \boxed{3} \\ \text{Risk Level} \end{array}$$

Event B

$$\begin{array}{c} \boxed{4} \\ (S) \end{array} \times \begin{array}{c} \boxed{1} \\ (F) \end{array} \times \begin{array}{c} \boxed{1} \\ (D) \end{array} = \begin{array}{c} \boxed{4} \\ \text{Risk Level} \end{array}$$

Overall Risk Level:

$$\boxed{4}$$

Risk Assessment #E1

Change Description in Detail:

Changes in media fill program
- Change in design (e.g. number filled, duration, interventions, shift changes, number of personnel, etc.)

Assumptions and Comments:

The new design change incorporates all the typical interventions, personnel activities and aseptic manipulations that impact sterility assurance and is in accordance with the FDA 2004 Aseptic Guidance

Possible Events:

(Negative events that could occur as a result of the change)

A. Media Fills (Process Simulations) do not have a direct impact on product quality as no product is filled, but rather provide an indirect evaluation of the filling operations performance on sterility

Type of Data Needed to Support the Change:

A. Justification that the new media fill design adequately simulates the process

Overall Risk Level:

NA

While a risk level could not be completed using the risk assessment scale developed, this area was identified by the team as an area where additional clarity regarding reporting expectations would be beneficial.

Risk Assessment #E2

Change Description in Detail:

- | |
|--|
| Changes in media fill program <ul style="list-style-type: none">- Change in media- Change in incubation parameters- Change in methods of media sterilization |
|--|

Assumptions and Comments:

- | |
|--|
| <ul style="list-style-type: none">- The new media used in media fill is capable of supporting the growth of USP microorganisms and recovering the typical known environmental isolate(s) detected in the manufacturing environment.- The duration of the incubation is at least 14 days, and temperature is within the range of 20-35°C- The change may involve change from 2 temperatures to 1 temperature, or in the sequence of high/low temperature incubation- Change in methods of media sterilization: steam sterilized or filter sterilized |
|--|

Possible Events:

(Negative events that could occur as a result of the change)

- | |
|---|
| A. Media fills (process simulations) do not have a direct impact on product quality as no product is filled, but rather provide an indirect evaluation of the filling operations performance on sterility |
|---|

Type of Data Needed to Support the Change:

- | |
|---|
| A. <ul style="list-style-type: none">- Growth promotion studies (USP panel organisms and EM isolates) to demonstrate the acceptability of the new media- Data to show the new incubation parameters are capable of detecting USP panel of challenge organisms and environmental monitoring isolates- Proper sterilization validation data to demonstrate sterility of the media |
|---|

Overall Risk Level:

NA

While a risk level could not be completed using the risk assessment scale developed, this area was identified by the team as an area where additional clarity regarding reporting expectations would be beneficial.

Risk Assessments Format #E3

Change Description in Detail:

Changes in microbiological test methods for water, environmental monitoring, raw material, components, identification and in-process bioburden

Assumptions and Comments:

- Method sensitivity/accuracy increases or is equivalent

Possible Events:

(Negative events that could occur as a result of the change)

A. Change in a test method with increased or equivalent sensitivity/accuracy does not have a direct impact on product quality as related to the manufacturing operation as no manufacturing process change is occurring

Type of Data Needed to Support the Change:

A. - Method validation

Overall Risk Level:

NA

While a risk level could not be completed using the risk assessment scale developed, this area was identified by the team as an area where additional clarity regarding reporting expectations would be beneficial.

RECOMMENDED REPORTING LEVELS

The following table outlines the Working Group's recommendations for the level of reporting based on the level of risk using current reporting categories.

Overall Risk Assessment Value	Suggested Reporting Category
0 – 4	Annual Reportable
5 – 16	CBE (CBE to CBE-30)
17 – 48	Prior Approval

APPENDIX I

APPROVED WORK PLAN

(Work Plan and Working Group Members Approved September 2005)



Project Name: **Post Approval Change Guidance for Sterile Products**

Name of Working Group: **PAC – S**

Technical Committee: **Manufacturing TC**

TABLE OF CONTENTS

I. BACKGROUND..... 120

II. GUIDANCE OR REGULATION TO BE ADDRESSED..... 121

III. DESCRIPTION OF OBJECTIVE..... 122

IV. POTENTIAL IMPACT 122

V. WORK PLAN OUTLINE..... 122

VI. WHAT WILL BE IN THE FINAL REPORT 123

VII. DETAILED WORK PLAN 123

I. BACKGROUND

There is currently not a post approval guidance document specific to the manufacture of sterile drug product. The development of such a guidance would be in line with the FDA's move to a more risk based approach as it would identify specific types of change, the risk associated with each and the corresponding filing requirement.

The FDA currently has 11 active guidance documents for CM&C Post Approval Change. Four (4) of the 11 are general guidance documents:

- “Changes to an Approved NDA or ANDA” April 2004
Note: Two supportive guidance documents for guidance have also been issued:
 - “Changes to an Approved NDA or ANDA: Questions and Answers” January 2001
 - “Changes to an Approved NDA or ANDA; Specifications – Use of Enforcement Discretion for Compendial Changes” November 2004
- “Changes to an Approved Application for Specified Biotechnology and Specified Synthetic Biological Products” July 1997

The remaining 7 were developed to provide additional detailed guidance for specific areas:

- “BACPAC I: Intermediates in Drug Substance Synthesis” February 2001
- “PAC-ATLS: Post approval Change – Analytical Testing Laboratory Sites” April 1998
- “SUPAC-MR: Modified Release Solid Oral Dosage Forms Scale-Up and Post approval Changes: CM&C; In Vitro Dissolution Testing and In Vivo Bioequivalence Documentation: Post approval Change – Analytical Testing Laboratory Sites” October 1997

Note: One supportive guidance document for this document has also been issued:

- “SUPAC-IR/MR: Immediate Release and Modified Release Solid Oral Dosage Forms Manufacturing Equipment Addendum” January 1999
- “SUPAC-SS: Nonsterile Semisolid Dosage Forms; Scale-up and Post-Approval Changes: CM&C; In Vitro Release Testing and In Vivo Bioequivalence Documentation” May 1997
- “SUPAC-IR: Immediate Release Solid Oral Dosage Forms: Scale-Up and Post approval Changes: CM&C, *In Vitro* Dissolution Testing, and *In Vivo* Bioequivalence Documentation” November 1995

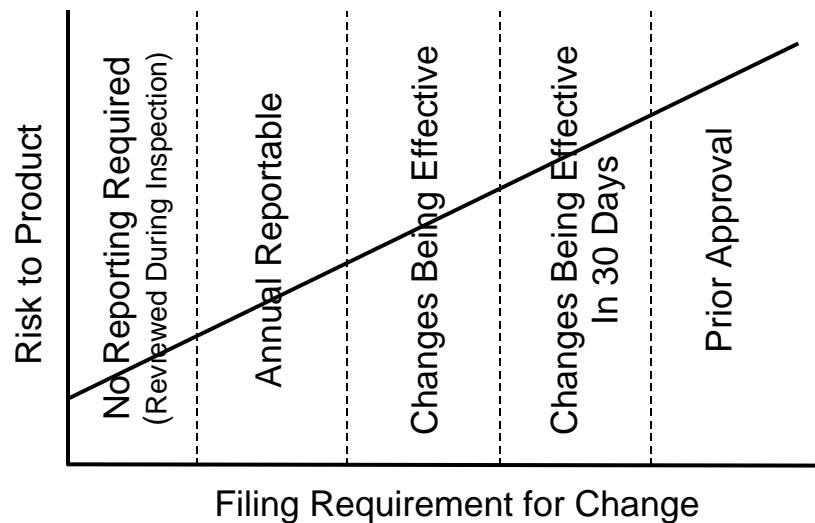
Note: Two supportive guidance documents for this document have also been issued:

- “SUPAC-IR Questions and Answers about SUPAC-IR Guidance” February 1997
- “SUPAC-IR/MR: Immediate Release and Modified Release Solid Oral Dosage Forms Manufacturing Equipment Addendum” January 1999

These additional guidance documents are extremely helpful in identifying:

- Specific types of changes
- The Classification of the specific changes (minor, moderate, major).
- The Data needed to evaluate the specific change.

This additional detail allows reporting that reflects the level of risk associated with specific changes. The greater the risk is, the greater the filing requirement.



In many cases, this allows for a lower reporting requirement than is recommended in the more general guidance documents because changes that were grouped together into more general categories would be evaluated individually.

There is currently not a post approval guidance document specific to sterile products. The development of such a guidance would be in line with the FDA's move to a more risk based approach as it would identify specific types of change, the risk associated with each and the corresponding filing requirement.

II. GUIDANCE OR REGULATION TO BE ADDRESSED

- Regulation 21 CFR Sec. 314.70 "Supplements and other changes to an approved application," and 21 CFR Sec. 601.12 "Changes to an approved application".
- Guidance document "Changes to an Approved NDA or ANDA" April 2004
- Guidance document "Changes to an Approved Application for Specified Biotechnology and Specified Synthetic Biological Products" July 1997
- "Changes to an approved application: biological products" July 1997

A post approval guidance document for sterile products would provide additional detail regarding specific changes, data required to support the change, and the appropriate reporting category.

III. DESCRIPTION OF OBJECTIVE

The PQRI Working Group for Reporting of Post Approval Changes for Sterile Products will work to develop a white paper containing a list of list of common changes that occur in the manufacturing of sterile drug products (drug substance manufacturing out of scope for this activity.) , a risk assessment of each change, recommendations on the level of reporting required, and recommendations on the data set to be submitted to support the change. The changes covered would be those specific to the manufacturing process and facility for sterile drug process. The composition of the group will be made up of experts from the FDA, industry, and academia.

IV. POTENTIAL IMPACT

The output will provide suggested content for a guidance on post approval change reporting that will be risk based. The development of such guidance would provide a clear understanding of the reporting categories for specific changes and the data set needed to support the change. By outlining the required data set for a given change, the guidance may provide for a lower reporting level contingent on the applicant providing the appropriate risk-based information. In some cases certain types of specific changes that today require a high reporting category due to the general nature of the guidance may be determined to be lower in risk as they are evaluated individually and therefore would require a significantly lower reporting category or in certain instances no reporting.

V. WORK PLAN OUTLINE (Revised based on Working Group's start date)

- Sept. 21, 2005 - Working group members identified and work begins.
- Oct 31, 2005 - Draft list of changes to be included identified and agreed upon by the working group.
- Nov 7, 2005 - Draft list of changes will be posted to the PQRI web site for 30 calendar days for comment.
- Nov 7, 2005 - Working group begins developing a risk assessment for each change.
For each change:
 - A risk assessment will be developed using a standard format agreed to by the working group.
 - As part of the risk assessment a numerical value will be applied to represent the risk posed by the change.
 - The data set required for each change will be developed.
- Dec 19, 2005 - The working group completes a review of all comments received and develops the final list of changes to be included in the activity.
- May 20, 2006 - Working group finishes risk assessments and data set requirements.
- May 20, 2006 - Working group begins applying suggested reporting requirements to each identified change.
- Jun 30, 2006 - Working group submits white paper for steering committee approval.

VI. WHAT WILL BE IN THE FINAL REPORT

The final report (White Paper) will include the list of changes, the data required to support the change with rationale, the reporting category, and the risk assessment used to evaluate the risk of the change.

VII. DETAILED WORK PLAN

The working group will develop a comprehensive listing of the types of changes to be included in the PQRI activity. The following is a general list of categories that may be used (the list provided is not intended to be all inclusive):

- Changes in the facility layout
- Changes in flow of personnel
- Changes in room classification
- Changes in manufacturing hold times
- Changes in in-process controls
- Changes in sterilizer loading patterns
- Changes in environmental monitoring
- Changes in batch sizes
- Changes in bioburden control strategy
- Changes in manufacturing sites
- Changes in the sterile filtration process
- Changes that bring older application files up to date
- Equipment changes
- Container/closure changes
- Components and composition changes
- Changes in the manufacturing process

After completing the list of changes to be included, the working group will begin reviewing each change by developing a risk assessment and a list of data required to support the change. The risk assessment will center on the potential of the change to negatively impact product quality. Based on the risk assessment, the agreed upon data requirements will be determined leading to a recommended reporting.

Listed below are the working group's deliverables:

- List of changes to be included
- Risk assessment for each change
- Data required to support the change
- Recommended reporting category

The working group will use the expertise within the working group to complete its tasks. There is minimal financial resources needed to complete the project and no data mining is planned.