



AAPS Workshop on Streamlining the CMC Regulatory Process

Microbiology Breakout Sessions
Summary
June 13, 2001

Rev. 5

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- Premise - The risk in making changes to sterile products is determined by the sterilization process, not by the molecule/product.
- Caveat - However, there is a hierarchy of preference for choice of sterilization technique and the properties of the molecule (and package) do determine how far down the hierarchy one must go. Therefore, there is a link between process and product.

Hierarchy of Sterilization Choices

Aqueous Formulations

- sterile filtered/aseptic process/terminally moist heat sterilized ($F_0 > 15$)
- sterile filter/aseptic process/bioburden based moist heat ($F_0 > 8$)
- terminally sterilized (only)
- sterile filtered/aseptic process/alternate (adjunctive) heat treatments
- sterile filtration/aseptic processing
- pre-sterilized components/aseptic processing

Non-aqueous liquid or dry powder

- dry heat 160°C for 120 minutes
- SAL of 10^{-6} via other times/temps
- ionizing radiation ($> 25 \text{ KGy}$)
- sterile filtration/aseptic processing
- pre-sterilized components/aseptic processing

note: other considerations apply

Low Risk
↑
↓
High Risk

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Questions for Audience:

1. Can we draw a line across each column, above which products could be 'low risk'?

YES

2. Is this formulation dependant?

NO in general, however,

If product is preserved or inherently anti-microbial, the line could be lowered.

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Questions (continued):

3. What changes to sterile products designated as 'low risk' should still require a supplement?

major change in sterilization technology

(e.g., filtration to gamma) requires prior approval

deleting a sterilization step

changing critical parameters/specs

going below "Ster Low Risk Line"

change to stopper compound that requires change to TS cycle

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Questions (continued)

4. What changes to sterile products designated as 'low risk' should be annual reportable?

changes giving equal or greater SAL, any change that stays above “low risk line”, minor* c/c changes (no change to c/c interface), changing process/equip using same valid. criteria, depyrogenation

*** What constitutes a “minor” c/c change? (open for continued input)**

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Questions (continued)

4. What changes to sterile products designated as 'low risk' should be annual reportable?

API change, analytical methods, equip. used prior to sterilization step, 0.2 to 0.1 micron filter, autoclave loading patterns, environ. monitoring, lyo cycle, resin changes, new filter supplier,

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Questions (continued)

5. For sterile drugs on the 'low risk' list - what chemistry changes have no microbio impact?

API changes

Sources of excipients

Equipment used prior to sterile filtration or after sealing

manufact. specifics prior to terminal sterilization (exception of hold times, unless preserved or anti-microbial?), mixing tanks, filling heads,

N₂ blanketing

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Questions (continued)

6. Any microbiological considerations for non-sterile products to be 'low risk'?

Solid or liquid orals, transdermals, suppositories, inherently anti-microbial products, non-aqueous - none

Transdermals, MDIs, dry powder inhalers, nasal inhalers
- may be microbiological constraints if classified as low risk

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GENERAL COMMENTS: These ideas can contribute to guidance for high and low risk as well

Is there a need for a periodic review of products that have been on the low risk list for X years.

The specific considerations applicable to steriles, may need to be addressed in guidance