Microbiological Quality of Drug Products after Penetration of the Container System for Dose Preparation Prior to Patient Administration

John W. Metcalfe, Ph.D.
Senior Review Microbiologist
FDA/CDER/OPS/New Drug Microbiology Staff

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Disclaimer

• The comments expressed today are those of the presenter only and do not necessarily represent the official positions or policies of the FDA.
Presentation Outline

• Introduction.
• Why are studies needed?- Nosocomial infection history.
• Why are studies needed?- Guidance.
• What is needed?- Risk Assessment.
• How should studies be designed?
• Case Study Examples.
• Industry Questions.
New Drug Microbiology Staff - Role on Review Team

- The NDMS advises regulatory physicians and scientists in CDER on the microbiological risks associated with various manufacturing techniques and dosage forms and provides recommendations as to the suitability of product manufacturing processes and controls.
New Drug Microbiology Staff

• Pre-Approval Role
  – Part of review team: INDs, NDAs/Supplements.
  – Is the drug microbiologically safe for the patient?

• Post-Approval Role
  – Provide subject matter expertise to Office of Compliance, District Offices, other CDER offices during outbreaks &/or investigations.
NDMS Review of Label
- product prepared at clinic prior to patient administration.

• Assessment of the information provided to the pharmacist and clinician regarding product preparation.
  – e.g.: how many preparation and dilution steps prior to final product for administration to patient?
NDMS Review of Label
- product prepared at clinic prior to patient administration.

- Assessment of the storage conditions of final product post preparation.
  - What are the storage temperature(s)?
  - What are the storage times?
  - What are the diluents?

- Does the application contain data to support the storage conditions?
Sterile Product
Container Closure Penetration

• Assumption:
  During penetration of the container closure system, microbes may have been introduced into the drug product.
Microbiological Product Quality Following C/C Penetration

- Drug Product Immediately Administered

VS

- Drug Product Prepared & Held for a Period of Time Prior to Administration
Post Manufacturing Drug Product Preparation Prior to Patient Administration

• Product examples:
  – Solids that are constituted with a diluent.
  – Liquid admixtures.
Nosocomial Infection Examples: Microbial Contamination of MDV/SDV/Admixtures

  
  – Tested 68 MDVs, 17 SDVs & 11 admixtures.
  – 4 of 96 (4.17%) were contaminated following multiple use.
Nosocomial Infection Examples: Microbial Contamination of MDVs


  - Table summarizing outbreaks caused by MDVs from 1983-2002.
  - 27 different outbreaks caused by Gram + & Gram- bacteria, viruses, fungi and protozoa.
Nosocomial Infection Examples: Microbial Contamination Following Product Preparation

  – 62 cases of infectious disease.
  – 7 different hospitals.
Nosocomial Infection Examples:
Microbial Contamination Following Product Preparation


  “To prevent further outbreaks, the people administering the agents must fully understand the ability of these drugs to support microbial growth so as not to put the patients at risk.”
## Bacterial Growth: A Doubling of Cell Numbers Every Generation

<table>
<thead>
<tr>
<th>Time (minutes)</th>
<th>Division #</th>
<th>Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>20</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>40</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>60</td>
<td>3</td>
<td>8</td>
</tr>
<tr>
<td>400 (6.6 hours)</td>
<td>20</td>
<td>1,048,576</td>
</tr>
</tbody>
</table>

![Diagram showing bacterial growth](image)
Microbiological Product Quality of Sterile Products Prepared in a Hospital Pharmacy

• **A Function of:**
  – Will the final product support microbial growth under the conditions of the holding period?

• **If so, then the holding period should be limited.**
USP<797> Pharmaceutical Compounding-Sterile Preparations

• Provides recommended finished product storage conditions and holding periods for low-risk, medium-risk and high-risk compounded sterile preparations.

• Pertains to drugs made by pharmacy compounding-not NDA/ANDA/BLA products.
Microbiological Product Quality of Sterile Products Prepared in a Hospital Pharmacy

• **CDER Current Thinking:**
  – Finished product storage conditions and related holding periods should be product specific and supported by scientific data.
  – This is consistent with FDA’s “Safety First” initiative, and the ICH “Quality by Design” concept.
Guidance for Industry: ICH Q8 Pharmaceutical Development

• **Microbial Attributes, Section 2.5:**
  “Where relevant, microbial challenge testing under testing conditions that, as far as possible, simulate patient use should be performed during development and documented in this section.”
“Stability testing of the drug product after constitution or dilution, if applicable, should be conducted to provide information for the labeling on the preparation, storage condition, and in-use period of the constituted or diluted product. This testing should be performed on the constituted or diluted product through the proposed in-use period on primary batches as part of the formal stability studies at initial and final time points, and ....”
What Does CDER Want in Support of Final Product Holding Periods?

• A Risk Assessment Report.
The Risk Assessment Report Should Include:

- A short summary evaluating the constituted product’s formulation with regard to its potential to support microbial growth.
- Studies demonstrating whether the product does (or does not) support growth of adventitious microbial contaminants under the storage conditions.
Study Design
- Suggested Challenge Microbes:

• USP<51> Microbes.
• Typical Skin Microflora.
• Nosocomial Infection Microbes.
Study Design
- Inoculum Size:

• Small numbers to simulate contamination.

• The inoculum size should be measureable and repeatable.
Study Design
- Storage Conditions:

• The storage conditions [e.g.: diluent(s), storage temperature(s)] should simulate those described in the label.
Study Design
- Duration:

• Periodic sampling times should be performed and include time points that are 2-3 times that of the requested maximum hold time.
Case Study: A

• NDA: Antibiotic Powder.

• Proposed Label:
  – Constitution involved 5 aseptic transfers.
  – Diluents: Normal Saline OR 5% Dextrose.
  – Storage Conditions for final product in infusion bag:
    • Saline: 12 hours at RT and 72 hours at refrig.
    • Dextrose: 4 hours at RT and 48 hours at refrig.
## Case Study: A

<table>
<thead>
<tr>
<th>Diluent</th>
<th>Stability time (hours)</th>
<th>2-8°C (Refrigeration)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal saline</td>
<td>12</td>
<td>72*</td>
</tr>
<tr>
<td>5% Dextrose</td>
<td>4</td>
<td>48*</td>
</tr>
</tbody>
</table>

* Once removed from the refrigerator, infusions should be completed within the room temperature stability time, provided the total refrigeration time, time to reach room temperature and infusion time does not exceed total refrigeration stability time.
Case Study: B

- Same Applicant as Case Study A.
- Supplement calling for an extension of hold time from 24 hours to 72 hours under refrigeration & from 8 hours to 12 hours at room temperature for 0.9% sodium chloride constituted product ONLY.
Case Study: B
- Challenge Organisms

- Aspergillus niger
- Candida albicans
- Escherichia coli
- Pseudomonas fluorescens
- Staphylococcus aureus
Case Study: B
- Methods

• Test microbe inoculum target sizes: 25 CFU/mL in infusion bag.

• At selected time intervals, challenge organism concentration was determined by a membrane filtration method.
Case Study: B - Sample Data

Table 4: Microbial Recovery of Test Microorganism Staphylococcus aureus (ATCC 6538) in 0.9% Sodium Chloride Infusion Solution over Storage at 22.5 ± 2.5 °C

<table>
<thead>
<tr>
<th>Time (hrs)</th>
<th>cfu/mL</th>
<th>Log</th>
<th>Diff. (vs. t₀)</th>
<th>1 mL</th>
<th>Avg</th>
<th>4 mL</th>
<th>Avg/m</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>18</td>
<td>1.26</td>
<td>0</td>
<td>14</td>
<td>16</td>
<td>15</td>
<td>69</td>
</tr>
<tr>
<td>8</td>
<td>3</td>
<td>0.48</td>
<td>-0.78</td>
<td>6</td>
<td>3</td>
<td>5</td>
<td>12</td>
</tr>
<tr>
<td>16</td>
<td>2</td>
<td>0.30</td>
<td>-0.95</td>
<td>3</td>
<td>2</td>
<td>3</td>
<td>11</td>
</tr>
<tr>
<td>24</td>
<td>2</td>
<td>0.30</td>
<td>-0.95</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>9</td>
</tr>
<tr>
<td>48</td>
<td>1</td>
<td>0.00</td>
<td>-1.26</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>4</td>
</tr>
</tbody>
</table>
Case Study: B
- Sample Data

### Table 21: Microbial Recovery of Test Microorganism Candida albicans ATCC 10231 in 5% Dextrose Infusion Solution over Storage at 5.0 ± 3.0 °C

<table>
<thead>
<tr>
<th>Time (hrs)</th>
<th>cfu/mL</th>
<th>Log</th>
<th>Diff. (vs. t₀)</th>
<th>1 mL</th>
<th>Avg</th>
<th>4 mL</th>
<th>Avg/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>38</td>
<td>1.58</td>
<td>0</td>
<td>44</td>
<td>53</td>
<td>49</td>
<td>141</td>
</tr>
<tr>
<td>4</td>
<td>42</td>
<td>1.62</td>
<td>0.04</td>
<td>53</td>
<td>48</td>
<td>51</td>
<td>174</td>
</tr>
<tr>
<td>8</td>
<td>53</td>
<td>1.72</td>
<td>0.14</td>
<td>58</td>
<td>57</td>
<td>58</td>
<td>227</td>
</tr>
<tr>
<td>16</td>
<td>49</td>
<td>1.69</td>
<td>0.11</td>
<td>54</td>
<td>55</td>
<td>55</td>
<td>194</td>
</tr>
</tbody>
</table>
Case Study: B
- Conclusion

- Studies performed by applicant support an extension of the hold time for product constituted in normal saline, but not for product constituted in dextrose.

- The supplemental application calling for an increased holding period for product constituted in 0.9% sodium chloride was approved.
### Table 3: Storage and Stability Times of Infusion Solutions Prepared in Normal Saline or 5% Dextrose

<table>
<thead>
<tr>
<th>Infusion prepared in</th>
<th>Stability Time at Room Temp. (includes room temperature storage and infusion time)</th>
<th>Stability time at 2-8°C (Refrigeration) (includes refrigerator storage and infusion time)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal saline</td>
<td>8-12 hours</td>
<td>24-72 hours</td>
</tr>
<tr>
<td>5% Dextrose*</td>
<td>4 hours</td>
<td>24 hours</td>
</tr>
</tbody>
</table>

*5% Dextrose should not be used for infusion durations greater than 1 hour.*

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**Case Study: B - Current Label**
Case Study C: - Introduction

• Initial labeling information called for dilution of the product in either:
  – Normal saline.
  – 5% dextrose in water.
  – Ringer’s lactate.

• Administer by infusion over 3.5 - 4 hours.
Case Study C:

- During review of the NDA, the Clinical Pharmacology reviewer recommended a longer infusion time than that proposed in the NDA.

- As a result of this recommendation, data were needed to demonstrate the final product does not support microbial growth during a longer infusion.
Case Study C: Amendment to NDA “Microbiological assessment was not considered …”

• “The infusion systems…are by their nature, a source of nutrients for microbial organisms. Therefore, any attempt to inoculate these systems would undoubtedly cause a significant increase in microbial counts, thus yielding a failed test.”
Case Study C

• The applicant contracted out the performance of the studies.
• Used a panel of 5 USP<51> microbes.
• Inoculated final solutions with a challenge of 10-100 CFU of microbe.
• 1 mL samples were removed at 0, 2, 4, 6, 8 and 24 hours.
• Membrane filtration: determine counts.
Case Study C

- Conclusion

• The data supported the necessary infusion times.

• Product label was modified as follows:
  – “The infusion solution should be prepared immediately before use, stored at not greater than 25C, and any portion of the solution remaining should be discarded 6 hours after preparation.”
Case Study D

- Antibiotic that is reconstituted in a variety of diluents.
- Storage of final product for up to 24 hours at room temperature or 72 hours refrigerated.
- A contract testing laboratory performed the study.
- Applicant reported: “The gram-negative organisms exhibit growth at the time intervals and storage conditions tested” (including time-zero).
- Requested holding times were not allowed due to flawed studies.
- Be careful when designing and interpreting study.
Industry Questions Pertaining to CDER Post Constitution Policy

1. Is this a new policy?

No, the policy has been in place in CDER for decades. It evolved from the pharmacy bulk pack policy which limits the post penetration hold time unless a firm presents data in the application which demonstrate that the hold time may be extended.
Industry Questions Pertaining to CDER Post Constitution Policy


2. While this article seems to be specific to non-preserved products, several of the references and ICH Q8 are referring to multi-dose and/or preserved products.

**Answer:** the references to multiple dose products were made to illustrate the concept of product contamination during use.
Industry Questions Pertaining to CDER Post Constitution Policy


3. Several of the articles also are directly related to using improper aseptic technique, or dosing the product off label and doesn’t conclude that a higher level of microbial risk management is due the manufacturer but those preparing/using the product.

**Answer:** We agree and understand that products are mishandled in clinical settings.
Industry Questions Pertaining to CDER Post Constitution Policy


4. Where does USP<797> fit in?

Answer: USP<797> pertains to pharmacy compounding and therefore does not fit in with this discussion. The beyond-use-dates provided in <797> do not apply to NDA or ANDA or BLA products.
Industry Questions Pertaining to CDER Post Constitution Policy


5. “The feeling I get from this is that FDA does not seem to have much confidence in the final preparers ability to aseptically prepare the final product and that the pharmaceutical company should provide due diligence for its product using that supposition.”

Answer: FDA understands that contamination happens. Show us your product does not support growth, or shorten the labeled holding period.
Industry Questions Pertaining to CDER Post Constitution Policy

PDA Global Conference on Pharmaceutical Micro (DC; Oct 2010).

6. Where do the study acceptance criteria come from?

Answer: USP<51> definition of no increase.
Industry Questions Pertaining to CDER Post Constitution Policy

PDA Global Conference on Pharmaceutical Micro (DC; Oct 2010).

7. Why was this published in a paper and not in a Guidance for Industry?

A guidance takes a long time to complete. This was an effort to be transparent with a policy that we were dealing with one application at a time.
Industry Questions Pertaining to CDER Post Constitution Policy

Email Inquiry to Metcalfe (June 2011).

8. A generic manufacturer is matching the RLD in all aspects, formulation details as well as diluents to be used. Why does microbial study in diluents become necessary for the generic manufacturers?

The RLD manufacturer may not have performed the microbiological studies at the time of initial approval of the NDA.
In Conclusion

• A product specific, risk based, scientific approach to the development of holding periods should be taken for sterile non-preserved products prepared in the clinical setting.

• This includes reconstitution, admixing and withdrawing doses for administration later.
THANK YOU

Further Info:
American Pharmaceutical Review Paper
Jan/Feb 2009.

Email: john.metcalfe@fda.hhs.gov

Phone: 301-796-1576