BACKGROUND

Typically, parenterally administered products for clinical studies must be manufactured under GMP conditions. However, when reconstitution for injection can be performed under USP <797> Clean Room conditions by licensed pharmacists, sterility can be achieved at the clinical facility, potentially reducing the duration of finished product stability and sterility data required to enable dosing. USP <797> is a general chapter in the USP that describes requirements for the preparation of sterile drugs, including radio-pharmaceuticals. The rationale for USP <797> is to prevent harm and fatality to patients that could result from microbial contamination and excessive bacterial endotoxins. The regulations apply to healthcare institutions, pharmacies, physicians’ offices, and other facilities where compounded sterile preparations are prepared.

PURPOSE

The purpose of this study was to determine whether sterile compounding of non-sterile radiolabeled API can result in a sterile finished product appropriate for parenteral administration in ADME and microtracer studies. The purpose of this study was to determine whether sterile compounding of non-sterile radiolabeled API can result in a sterile finished product appropriate for parenteral administration in ADME and microtracer studies.

METHODS

The study included the preparation and testing of:

- A mock preparation using unlabeled API (Lot 1)
- A preparation using radiolabeled API (Lot 2)

Both preparations were prepared and handled in the same manner to minimize variability except for minor differences in the weight of the API. The preparations consisted of weighing 12.8 mg of API into a 100 mL, depyrogenated sterile vial and reconstituting with 100 mL sterile water for injection followed by sonication.

Sterile filtration of the API solution was conducted in a Labconco Purifier® Logic® Class II Type A2 biological safety cabinet within a USP <797> Clean Room. Both the biological safety cabinet and the USP <797> Clean Room are certified every six months with sterility testing.

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RESULTS OVERVIEW

Preparation with filtration resulted in a sterile, endotoxin free solution acceptable for administration to human participants by IV infusion. The product successfully qualified for USP <797> EP6.1.2/CIF-R10.12. The results of the mock preparation (Lot #1) are summarized in Tables 1, 2 and 4. The results were similar for Lot #2 and are summarized in Tables 3 and 5.

CONCLUSIONS

Sterilization of non-sterile radiolabeled API can be achieved on-site for parenteral administration to human participants by licensed pharmacists in a USP <797> compliant Clean Room. On-site sterile formulation is an innovative alternative for clinical studies which require an IV formulation for a specific study. This approach will save time and money in drug development by eliminating very lengthy and costly manufacturing steps in the formulation process.

REFERENCES

1. USP General Chapter <797> Pharmaceutical Compounding – Sterile Preparations. United States Pharmacopoeia. 2010
3. USP General Chapter <797> Sterility Testing. United States Pharmacopeia. 2010

Table 1: Bacteriostasis and Fungistasis Sterility Qualification Testing

<table>
<thead>
<tr>
<th>Organism</th>
<th>Reference Plate DPU’s (Plate/Petri)</th>
<th>Medium</th>
<th>Specification</th>
<th>Result</th>
<th>Pass/Fail</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacillus Subtilis (B. subtilis)</td>
<td>(68/59)</td>
<td>TSB</td>
<td>Sample and fungal positive controls</td>
<td>Growth observed at day 3 for position control and sample</td>
<td>Pass</td>
</tr>
<tr>
<td>Aspergillus fumigatus/Aspergillus niger</td>
<td>(36/43)</td>
<td>TSB</td>
<td>Growth observed &lt; 5 days</td>
<td>Pass</td>
<td></td>
</tr>
<tr>
<td>Candida albicans</td>
<td>(18/47)</td>
<td>TSB</td>
<td>Bacterial Positive controls Growth observed &gt;3</td>
<td>Growth observed at day 3 for position control and sample</td>
<td>Pass</td>
</tr>
<tr>
<td>Clostridium perfringens</td>
<td>(47/72)</td>
<td>FTM</td>
<td>Growth observed &lt;3</td>
<td>Growth observed at day 3 for position control and sample</td>
<td>Pass</td>
</tr>
</tbody>
</table>

Table 2: Endotoxin Testing

<table>
<thead>
<tr>
<th>Test Date</th>
<th>Method: EP 2.6.14/USP Turbidimetric Method</th>
<th>Organism</th>
<th>Concentration</th>
<th>Results</th>
<th>Pass/Fail</th>
</tr>
</thead>
<tbody>
<tr>
<td>19 Mar 2012</td>
<td>EP 2.6.14/USP Turbidimetric Method</td>
<td>LPS</td>
<td>0.1 EU/mL</td>
<td>0.0987</td>
<td>Pass</td>
</tr>
<tr>
<td>20 Mar 2012</td>
<td>EP 2.6.14/USP Turbidimetric Method</td>
<td>LPS</td>
<td>0.2 EU/mL</td>
<td>0.0987</td>
<td>Pass</td>
</tr>
</tbody>
</table>

Concentration Coefficient absolute value greater than or equal to 0.999 Pass
Mean PPC must be within 50-200% of the known concentration of 105 EU/mL 95% @ the next concentration Pass
Negative Control must be below the lowest point of the curve LFM - 0.002 EU/mL
Test sample specification is "b信息 only" <0.005 EU/mL Pass