Establishing a Beyond Use Date for Compounded Norfloxacin Oral Suspension

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Abstract

Purpose: This study was conducted to determine a Beyond Use Date (BUD) for Compounded Norfloxacin Oral Suspension based on storage at ICH conditions for 60 days. The USP General Chapter <795> requires a BUD for all compounded pharmaceutical preparations. This data differs from a commercial product expiration date since compounded preparations are not subject to the same requirements for linearity, specificity and accuracy, repeatability, range, and ruggedness. The USP also requires that compounded preparations be assigned a Beyond Use Date (BUD) for stability and to prevent drug shortages.

The intent of this study was to determine a BUD for compounded Norfloxacin Oral Suspension based on the USP monograph for Norfloxacin. The HPLC method was developed for measuring norfloxacin in compounded oral suspensions.

Materials

Norfloxacin 400 mg tablets (Noroxin®) to 0.5 x 4X100, X4101 and X4102; Merck & Co., Inc., Whitehouse Station, NJ.

Methods

Compounding

The compounded oral suspension was prepared according to the protocol outlined in USP Chapter <797>, Pharmaceutical Compounding – Nonsterile Preparations. See Table 1 for a description of the preparation method.

HPLC Method Validation

The appropriateness of the chromatographic method conditions were evaluated by assessing the following performance parameters:

- Standard Stress Degradation
- Compound Preparation Stress Degradation
- Filter Compatibility
- Linearity
- Accuracy
- Repetitability
- Range
- Ruggedness

The method met or exceeded all validation criteria. An example chromatogram for the compounded preparation is shown in Figure 1 and the linearity standard curve is provided in Figure 2.

Results & Discussion

The stability data is presented in graphical format in Figures 3-6. The 95% confidence interval around the 20°C/60%RH stability data (Figure 4) indicates a predicted BUD of slightly under 60 days at 20°C/60%RH. This is determined by where the lower confidence interval curve crosses the lower specification limit of 90% of labeled content. All other conditions evaluated (Figures 3, 5 and 6) predict a BUD greater than 60 days. Based on these data, assignment of a 60 day BUD should be considered. Although the control room temperature was 25°C/60%RH, these data were marginal, and the exceptional accelerated data provide additional support for this conclusion.

Conclusions

Stability studies were conducted using three different batches of Compounded Norfloxacin Oral Suspension with a percent of label claim maintained between 90% and 104% which satisfies the proposed USP criteria (90.0% – 110.0%) for percent of label claim. The stability data support assignment of a 60 day BUD for Compounded Norfloxacin Oral Suspension in a 1:1 blend of Vehicle for Oral Solution, NF and Vehicle for Oral Suspension, NF.

Disclosures

- This work was supported by 2010 Grant Offering for Pharmaceutical Compounding from The United States Pharmacopeial Convention, Inc.
- Dr. Elder is a member of the 2010-2015 USP Compounding Expert Committee.
- The information, views and opinions presented here are entirely those of the authors independent work and do not necessarily reflect the views of USP.

Table 1. Storage Conditions and Stability Protocol

<table>
<thead>
<tr>
<th>Condition</th>
<th>BUD (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5ºC/30%RH</td>
<td>60</td>
</tr>
<tr>
<td>5ºC/70%RH</td>
<td>60</td>
</tr>
<tr>
<td>25ºC/60%RH</td>
<td>60</td>
</tr>
<tr>
<td>30ºC/65%RH</td>
<td>60</td>
</tr>
<tr>
<td>40ºC/75%RH</td>
<td>60</td>
</tr>
</tbody>
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Figure 1 – Example Norfloxacin HPLC Chromatogram

Figure 2 – Linearity Standard Curve

Figure 3 – 5ºC/30%RH Stability Data

Figure 4 – 25ºC/60%RH Stability Data

Figure 5 – 25ºC/60%RH Stability Data

Figure 6 – 40ºC/75%RH Stability Data

Figure 7 – Example Norfloxacin HPLC Chromatogram