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Application of Freethink's ASAPprime® Software to Analyze and Predict the Impact of Storage and Handling Temperature Excursions for Cold-Chain Handling of Netarsudil Ophthalmic Solution

Karen E Crews, Meg M Thompson

Aerie Pharmaceuticals, Inc.

CONTACT INFORMATION: kcrews@aeriepharma.com

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PURPOSE

Netarsudil Ophthalmic Solution (Rhopressa®) is a topical ophthalmic solution that is stored refrigerated, but that is used by the patient at temperatures up to 25°C for up to 6 weeks. The purpose of this study was to predict maximum storage and handling temperature excursions that would not significantly impact the product stability and hence maintain quality of the drug product within specification until end of use by the patient. ASAPprime® was used to predict the stability of the drug product under various temperature conditions.

METHODS

Extensive stability data has been generated for Netarsudil Ophthalmic Solution, including 36 months at 2-8°C, 6 months at 25°C/40% RH, 3 months at 30°C/65% RH and 1 month at 40°C/20% RH. Two specified impurities (AR-13323 and AR-13712) were observed to change on stability. These two impurities had an increase of approximately 40% relative to the drug product specification after 6 months at the accelerated stability condition of 25°C/40%RH. No other stability-indicating tests showed significant change after samples had been stored at long-term and accelerated storage conditions. Stability data were generated using drug product batches which started with initial impurity levels at the method limit of quantitation (<0.10%).

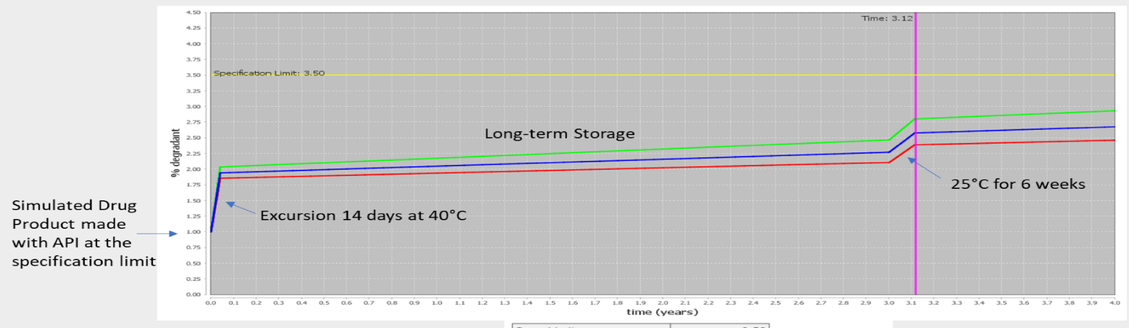
Initially, the individual impurity results for AR-13323 and AR-13712 from 36 months of long-term and accelerated testing conditions were entered into ASAPprime Software. It was desired to examine the potential impact on stability should the initial impurity profile of the drug product be closer to the maximum input drug substance specification for these impurities. Data used for modeling were modified to represent the worst-case scenario for drug product by applying the sum of the drug substance specification limit and the actual level of impurity from drug product stability studies results. Then, stability data were evaluated using the excursion function of ASAPprime to determine the impact of a sequence of temperature excursions.

RESULTS

The ASAPprime analysis applied to the modified impurity stability data predicted that the drug product would remain within specification for the proposed life of the product. The specific storage and handing excursions which were predicted by ASAPprime to provide a stable drug product are: 40°C for 14 days, 2-8°C for 3 years, and 25°C for 6 weeks. The results show the impurity levels of the drug product are predicted to be below the specification limit even when the input drug substance is at the specification limit for the drug substance.

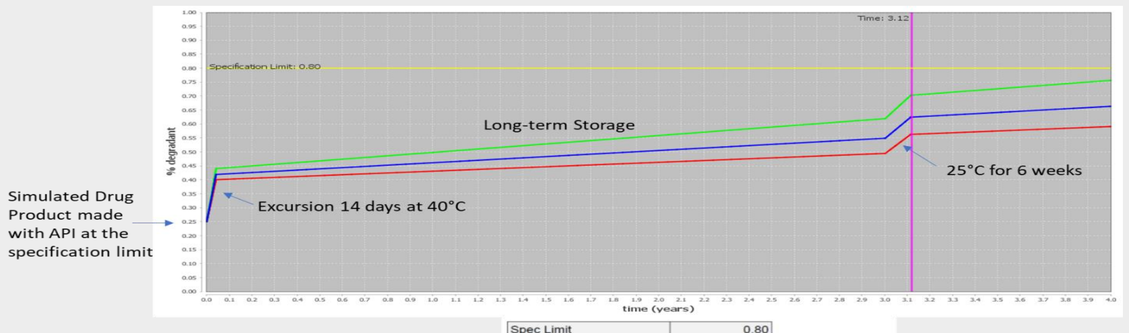
These data support the FDA-approved label including a storage statement of "Store at 2°C to 8°C (36°F to 46°F) until opened. After opening, the product may be kept at 2°C to 25°C (36°F to 77°F) for up to 6 weeks. During shipment, the bottle may be maintained at temperatures up to 40°C (104°F) for a period not exceeding 14 days."

Figure 1: ASAPprime excursion predictions for AR-13323 using modified stability data



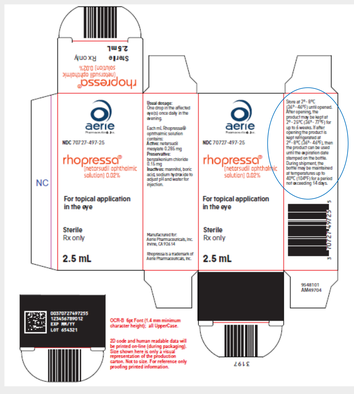
Spec Limit	3.50	
Median Shelf-Life	> 4.00	years
Probability of Passing	99.99	%
Mean Kinetic Temperature	14.12	° C

Figure 2: ASAPprime excursion predictions for AR-13712 using modified stability data



Spec Limit	0.80	
Median Shelf-Life	> 4.00	years
Probability of Passing	98.09	%
Mean Kinetic Temperature	12.07	° C

Figure 3: Rhopressa commercial package showing storage and handling conditions which were derived from ASAPprime modeling



CONCLUSIONS

Netarsudil Ophthalmic Solution met specification after 3 years storage at 2-8°C and subsequent use for up to 6 weeks at temperatures of 2-25°C. As shown in this evaluation, the degradation impurities AR-13323 and AR-13712, even after cumulative storage temperature excursions at 40°C for a period of 14 days, with drug product manufactured using drug substance already at its specification limit, are within drug product specification limits, and the product itself is expected to meet specifications after 3 years long-term storage and then 6 weeks in-use at temperatures up to 25°C.

The excursion function within ASAPprime predicts that AR-13323 and AR-13712 have a 100% and 98% probability, respectively, of meeting the specification, even when product is made using drug substance at the individual impurity specification limits. The storage and handling excursions predicted by the ASAPprime analysis have been approved by the FDA for Rhopressa.

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