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Short communication

Thermal-cycling stress studies to support transport and distribution of liquid dosage forms

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Introduction

Stability is defined as the capacity of a drug product to remain stable within established specification to maintain its identity, strength, quality and purity throughout expiration dating periods. Although the storage conditions are relatively constant, the distribution environment can vary greatly, especially when a drug product is shipped between various climatic zones. Seasonal changes, mode of transportation, and the number of drop-off points are also variables that should be considered within the pharmaceutical supply chain. Drug product requiring controlled-temperature storage conditions must be distributed in a manner that ensures that the product quality will not be adversely affected.Some of the information necessary for understanding the quality impact of temperature excursions, especially those that involve multiple shipment legs and excursion events, may be gathered from thermal-cycling stress studies. Studies on a drug product that is pre-exposed to temperature cycling under high and low temperature conditions may be useful in determining the impact on product quality from an excursion where the product is exposed to multiple temperature stress conditions. Since international distribution of drug product may include multiple distribution legs, thermal-cycling studies should be designed with a minimum of three cycles to support cumulative exposure periods from the entire distribution process. The stability program is depending of the product sensitivity to environmental conditions. The final sensitivity of the product to environmental conditions is determined by its content and the container.

The aim of the presented study is to support the excursions that may occur during storage, transportation and distribution of the finished drug product.

Materials and methods

Materials

Methadone hydrochloride 10 mg/mL concentrate for oral solution is a product of Alkaloid AD Skopje and the batch analyzed during the thermal-cycling study were manufactured and packed in Alkaloid AD Skopje. Primary packaging is consisted of brown glass bottle sealed with screw cap PP 28 child resistant tamper evident ring with embossing and liner. For our thermal-cycle stress study two glass bottles of 1000 mL were used.

Methods

For performing the study, product is placed in the chosen transport container during a period of time corresponding to the longest anticipated transport duration. Data from critical quality parameters were collected after stored at each temperature to evaluate any changes that may occur within the finished drug product. Based on the previous knowledge for stability of the physical and chemical entity, two types of studies were conducted: Thermal and Freeze-Thaw studies were done by exposing the drug products to a few temperature cycles.

The ICH/WHO stability data guidelines define appropriate temperature ranges for the different study ranges −20°C ± 5°C, +5°C ± 3°C, 25°C ± 2°C, 30°C ± 2°C, 40°C ± 2°C, 50°C ± 2°C etc.

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Performed thermal-cycling stress study was consisted of 4 cycles, each cycle containing 3 different conditions for storage of our product and it was kept at the prescribed condition for 2 days. First condition was chosen to be −20°C ± 5°C; second condition was +5°C±3°C and the third condition was set at 50°C±2°C.

After prescribed days at each temperature, the samples and placebo were evaluated for selected critical quality parameters (CQPs). The parameters considered as critical for the respective drug product are: Appearance, Color, pH value, Assay of the active pharmaceutical ingredient (API) and Sodium benzoate (preservative), Related and degradation products. Viscosity and microbiological quality were evaluated at the end of each cycle. In order to investigate the possible presence of Benzene in Methadone hydrochloride (according to scientific literature) withdrawn from different thermal cycling monitoring conditions were analyzed at the end point of the stability excursion period. Validated stability-indicating methods were used for determination of the assay of Methadone hydrochloride and Sodium benzoate and related and degradation products.

Results and discussion

The results of the stability study to support distribution conditions on one batch of Methadone hydrochloride 10 mg/mL concentrate for oral solution, stored on multiple brief exposure to low, medium and high temperature stress conditions, show that all tested parameters, whether physical or chemical, remain stable throughout the duration of the cycling study.

The pH value, viscosity, color and appearance of the samples remain stable over the thermal-cycling study period. No crystallization is occurred in drug product.

The assay values for the active compound, as well as for the preservative, remain within the shelf-life specification during the studies. Results obtained from the parameter Related and degradation products meet the acceptance criteria. Mass balance values were achieved; usually 98-102% should be reached by adding assay value and levels of degradation products.

Microbiological quality testing showed that the product remains within the specification limits during all cycles.

The obtained GC-FID data show that there were no evidence about formation of Benzene from Sodium benzoate, neither in the Methadone hydrochloride 10 mg/mL concentrate for oral solution.

Additionally, in order to see the distribution of the data, SixGraph and MR charts were created with normal probability plot and the capability histogram for the parameters Assay of Methadone hydrochloride and Assay of Sodium benzoate for all temperatures in every cycle mentioned above, using the software STATISTICA. After the statistical evaluation it was concluded that no OOT results were observed.

Conclusion

After statistical evaluation of the content of the API and the preservative and related and degradation products it can be concluded that all of the evaluated results are within the limits of six sigma measurements between ± 3 standard deviations of the mean value.

All CQPs for this drug product remain within the shelf-life specification during the thermal-cycling study and no physical and chemical changes were detected. Nevertheless, in order to avoid any kind of damage of the primary packaging at extremely low temperatures (-20 °C), we recommend that the finished drug product should be stored and transported at ambient conditions with tolerated temperature excursions between +5°C and +50°C and additional storage advice should be added: Do not freeze.

References

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