QUALITY RISK MANAGEMENT IN THE ELABORATION OF HOLDING TIME STUDY OF ORAL SOLID PRODUCTS

Monção-Meireles, A.B.[1*]; Barros, T.G.[2], Macedo, E.V.[2]

[1]*Student of PGMA, Federal Fluminense University/Faculty of Pharmacy, Dr. Mario Viana Street, 523, Santa Rosa, Niterói, RJ. Brasil.*

[2]*PhD, Professor of PGMA/ Federal Fluminense University/Faculty of Pharmacy. Dr. Mario Viana Street, 523, Santa Rosa, Niterói, RJ. Brasil.*

**andrew.meireles@id.uff.br*

Introduction

During the manufacturing process, holding times may be stipulated in the process to obtain the final drug product. The intermediate material can be held from the subsequent step for various reasons, such as logistical priority, equipment maintenance or investigation of deviations[1]. During this time, the drug is subjected to impacts on its critical quality attributes (CQA)[2]. Therefore, an adequate risk management is required to assess the risks inherent to the process and the storage time on the CQAs, so that a mitigation and control strategy can be organized[3]. The aim of this work is to propose a holding time study applicable to oral solid products using the quality by design approach.

Material and Methods

This work used a case study methodology. For that end, first of all, it was necessary identify the state of the art with a literature review, followed by an evaluation of the technical documentation and elaboration of the risk analysis in order to determine the CQAs that were monitored during the study, the holding duration and sampling interval. Finally, a flowchart was drawn up to determine the steps of the process where the holding time should take place, alongside its duration.

Results and Discussion

The state of the art was reached through a qualitative and non-systematic search on the proposed theme. In this way, scientific articles, guides and legislation were consulted that provided the basis for the theoretical knowledge to propose the protocol model. The determination of the state of the art made it possible to generally determine the critical stages of processes, the recommended average times and the storage conditions so that it was possible to make a critical evaluation of the study in question.

Then, the technical documentation of the development of the product in question was consulted so that the state of the art was applied with the peculiarities of the product. Following, the product CQAs and the steps that allow the process to be paused were listed. With the CQAs identified, a multidisciplinary risk analysis was prepared to assess the risk of the holding time, storage conditions and environmental conditions on these attributes at each stage of the process, and thus determine the control points. Thus, the control points determined for the process were:

- after weighing;
- after sieving;
- after preparing the granulating solution;
- after wet granulation;
- after dry sizing;
- after final blend;
- bulk product.

The environmental conditions determined for the intermediate product were stricter than for the finished product.

The recommended storage conditions for both the intermediate and the bulk product were the same as those practiced for products in general, since the product was as stable as most oral solids.

A process flowchart was prepared with all the manufacturing steps and the proposed holding time periods to determine the monitoring steps that are critical control points. Table 1 summarizes the determined critical control points and the holding time purposed.

Table 1. Process stages, holding-time periods and CQAs.

Process stage	Holding- time period	CQA
after weighing	5 days	Appearance Water content Loss on drying (when applicable) Microbiological property
after preparing the granulating solution	24h	Appearance Microbiological property
after dry sizing	3 days	Appearance Loss on drying Microbiological property
after final blend	10 days	Appearance Assay Loss on drying Microbiological property
bulk product	6 months	Appearance Disintegration Dissolution Related substance Assay Loss on drying Microbiological property

Finally, the protocol was elaborated assigning the responsibilities, methods, sampling and the acceptance criteria.

Conclusion

The present work shows a successful protocol elaboration strategy for a holding time study applicable to oral solid products.

Acknowledgments

I thank my advisors and PGMA/UFF for the opportunity and encouragement.

Bibliographic References

[1] WHO. Annex 4 - General guidance on hold-time studies. WHO Technical Report Serie, v. 992, 2015, p. 87–93.

[2] PAWAR, D. P.; SHAMKUWAR, P. B. Evaluation of hold time of cetirizine di-hydrochloride compressed tablets. Drug Invention Today, v. 4, n. 12, 2012, p. 649–651.

[3] FDA. Guidance for Industry Q9 Quality Risk ManagementCenter for Drug Evaluation and Research.