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Development of an Investigation Strategy for Assay Performance

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INTRODUCTION

Recently, the process performance of the assay of Product A was assessed as statistically poor. An assay mean value below target (non-centered process) and the inter-batch variability leads to control limits close to or at internal release limits (IRL) (see Figure 1).

The purpose of the thesis is the investigation of the assay performance of Product A and the development of an investigation strategy to assess the assay performance, regardless of the product.

The manufacturing process was investigated from the dispensation of the raw materials towards the bulk drug product. The manufacturing consists of several steps. The most important are: dispensation, granulation, drying, compression and coating. In addition, the analytical method of the assay determination was investigated.

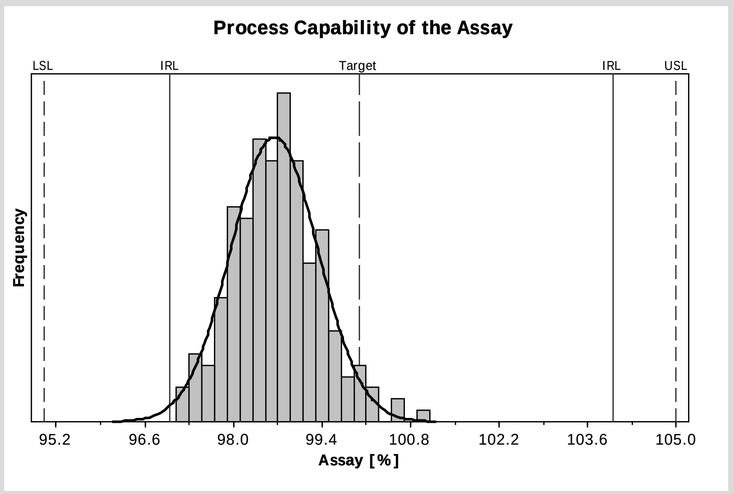

Fig. 1: Assay Capability of Product A

CONCEPT

The 6M-Model [1] was used to sum up hypotheses in a systematic way. The whole manufacturing process including dispensation and analytics of the assay was assessed.

The hypothesis, that a selective drug substance loss occurs during the manufacturing, was investigated with a batch screening. Any areas, where a loss of yield occurs, were determined. Samples were taken from the deposits and from the blend between the different manufacturing steps to localize any specific loss of drug substance.

Process and control parameters, which are possibly related to the assay of the bulk product, were assessed with a statistical data analysis.

From the experiences an investigation strategy was developed to address cases which need improvement of the assay performance, regardless of the product (see Figure 2).

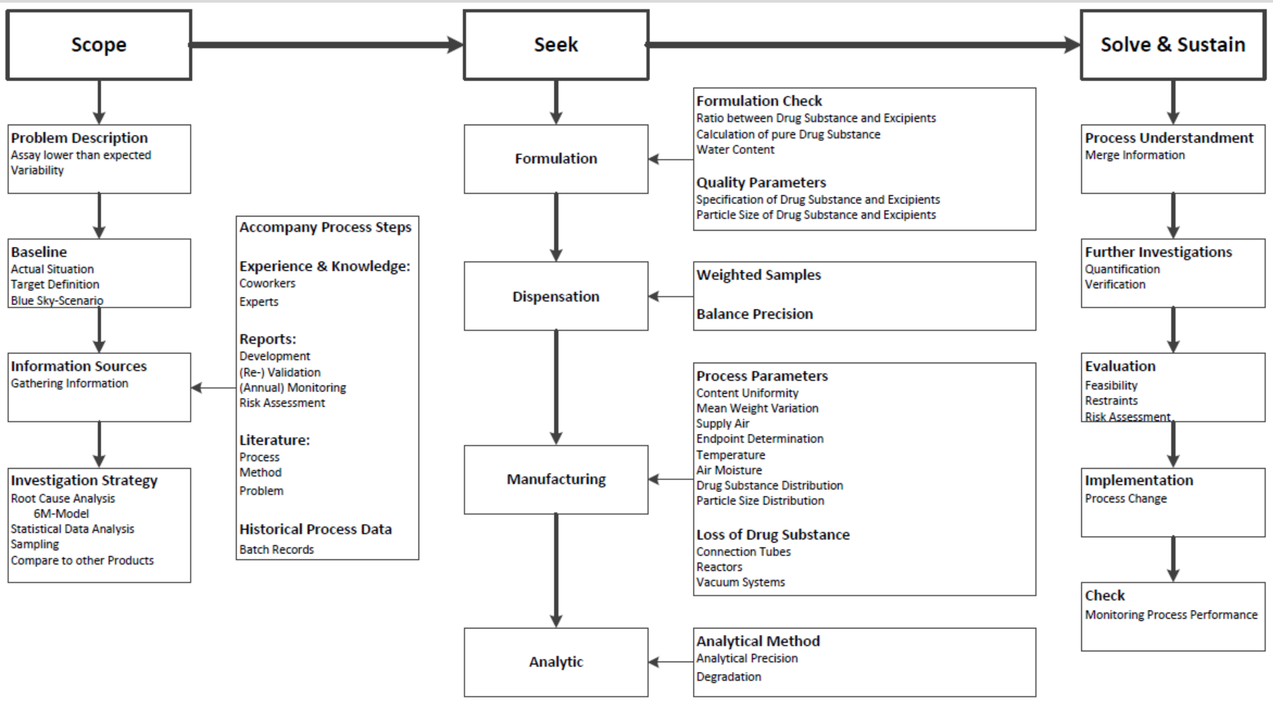

Fig. 2: Investigation Strategy: Assay Performance

Different root causes were identified. Due to the results further investigations were planned to improve the granulation and fluid bed drying process.

According to the results of the investigations different process changes were evaluated to improve the assay performance.

RESULTS

Figure 3 presents the sources of influence on the mean value and the variability of the assay.

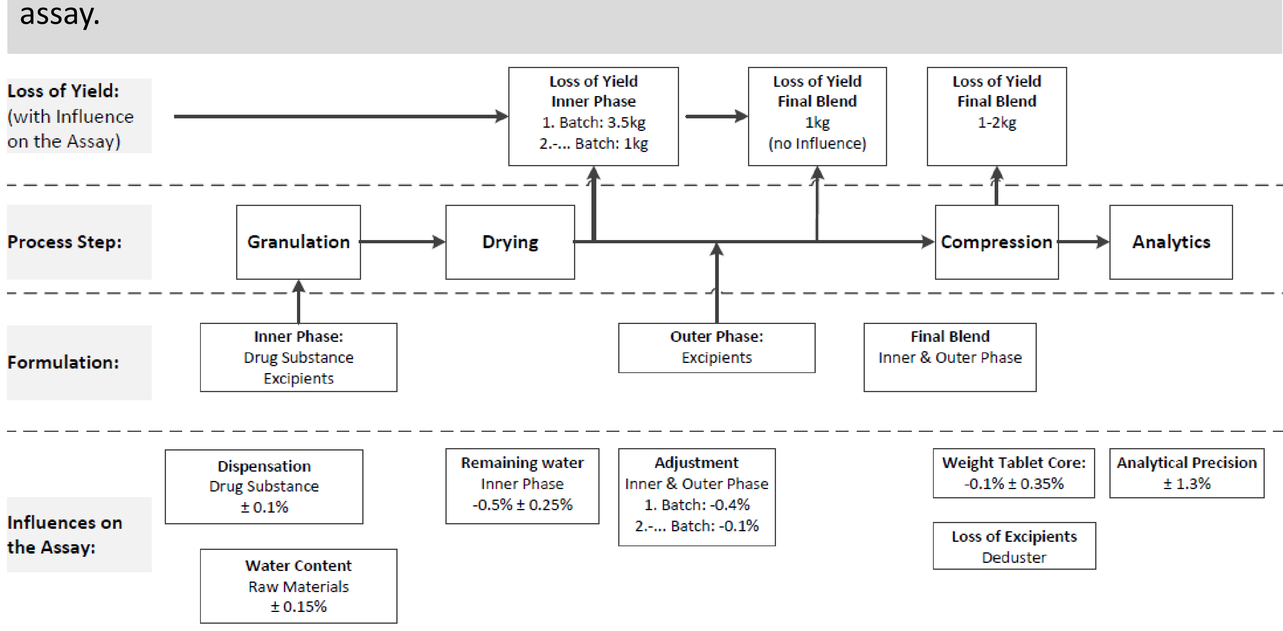

Fig. 3: Process Flow Analysis

Major Sources of Influence: Assay Mean Value

- Water Content of the Blend
- Adjustment of Inner- & Outer Phase

Major Sources of Influence: Assay Variability

- Water Content of the Blend
- Weight of the Tablet Cores
- Analytical Precision

Some of the water added to the blend during the granulation process is not completely removed during the drying process. This leads to a change between the targeted ratio of drug substance and excipients. Further investigations were performed to improve the drying of the blend. Therefore, the drying was prolonged and the fluidization of the blend was assessed.

The adjustment of the outer phase to the yield of the inner phase is not executed, because the control limit of the manufacturing instructions was never reached. Partially, due to the fact that the remaining water in the blend, added at the granulation, is broadening the control limit. This leads to a lower final assay.

The mean weight of the tablet core is currently slightly below target. This leads to a lower final assay. Additionally, the variability of the mean weight of the tablet core is the major root cause for the variability of the assay besides the analytical precision.

The analytical method might have improvement potential in regard to the analytical precision.

CONCLUSION

The major influences on the assay mean value and the assay variability have been assessed in the thesis and an investigation strategy has been developed.

A prolonged drying will lead to a higher assay mean value. Additionally, a more careful adjusted mean weight of the tablet cores prior to start of the compression process may tighten the distribution of the weight of the tablet cores. These process changes will improve the assay mean value and the assay variability. The assay performance will be assessed as acceptable.

The assay and the loss on drying of the inner phase should be monitored to generate a rationale if further process changes are reliable and feasible.

If the process performance needs further improvement, the tablet core weight can be increased to target.

REFERENCES

[1] Ishikawa, K. (1986). *Guide to Quality Control (Industrial Engineering & Technology).* Quality Records, 2nd Edition.