A generic QbD Method Development Approach for a generic pMDI – Application for Sirdupla™ Uniformity of Delivered Dose methodology

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Summary

Analytical method development and validation is performed using a generic Quality by Design (QbD) framework for Life Cycle Management. This is analogous to the framework recommended for product development in ICH guidelines. All methodology has a defined Analytical Target Profile (ATP), a set of predefined objectives that defines performance requirements, and are subject to risk management and continuous improvement processes.

The methodology for uniformity of delivered dose (UoDD), or dose content uniformity (DCU), is a Critical Quality Attribute (CQA) of Orally Inhaled and Nasal Drug Products (OINDP). In line with the QbD paradigm, this critical variable was assessed by designed experiments to understand the performance of the Sirdupla™ generic product versus the Seretide® Evohaler® innovator product (Salmeterol / Fluticasone Propionate, 120 actuations).

The analytical method requires control of critical shake / fire parameters for the priming, dose collection and waste actuations. In this case the priming and dose collection actuations are performed by an analyst. Automation is used only for the waste actuations performed between the stages of container life where the dose collection actuations are performed. Automation could be extended to the priming/collection actuations, and even the sample recovery process, to exercise greater control. The optimised methodology demonstrates that the Sirdupla™ pMDI (pressurised Metered Dose Inhaler) product generates comparable UoDD data to the Seretide® Evohaler® innovator product. Method robustness can therefore be established at an early stage in the method and product development life cycle, delivering methodology demonstrably appropriate for the product lifespan which is subject to continuous improvement processes in line with the QbD paradigm.

Introduction

Analytical method development and validation is performed using a generic Quality by Design (QbD) framework for Life Cycle Management [1, 2, 3]. This is analogous to the framework recommended for product development in ICH guidelines [4], and is a regular practice within the pharmaceutical industry [5, 6, 7, 8, 9, 10, 11]. All methodology has a defined Analytical Target Profile (ATP), a set of predefined objectives that defines performance requirements, and are subject to risk management and continuous improvement processes.

The methodology for uniformity of delivered dose (UoDD) / dose content uniformity (DCU) is a Critical Quality Attribute (CQA) of Orally Inhaled and Nasal Drug Products (OINDP). In line with the QbD paradigm, this critical variable was assessed by designed experiments to understand the performance of the Sirdupla™ generic product versus the Seretide® Evohaler® innovator product (Salmeterol / Fluticasone Propionate, 120 actuations).

Methodology

Two Sirdupla™ product strengths were evaluated, a High Strength (HS) product in respect to Seretide® Evohaler® - 25/250 mcg/actuation Salmeterol / Fluticasone Propionate, 120 actuations – and a Medium Strength (MS) product in respect to Seretide® Evohaler® - 25/125 mcg/actuation Salmeterol / Fluticasone Propionate, 120 actuations. Samples were prepared at the Start, Middle and End of the pMDI container life (SOL, MOL, EOL) using Unit Spray Collection Apparatus (USCA), in accordance with Ph.Eur and USP guidelines [12,13] as shown in Figure 1. Two actuations are collected per test sample. While priming and collection actuations were performed manually, an MDI FD-10 instrument (InnovaSystems, New Jersey, USA) was used to automate the waste actuations between the stages of container life. Samples were then analysed by HPLC-UV (High Performance Liquid Chromatography – Ultra Violet detection) methodology validated in accordance with ICH guidelines [14], quantifying amounts of Salmeterol Xinafoate (SX) and Fluticasone Propionate (FP). Dose proportionality was demonstrated for these actives for all studies, hence only FP data are shown. Critical method parameters are listed in Table 1.

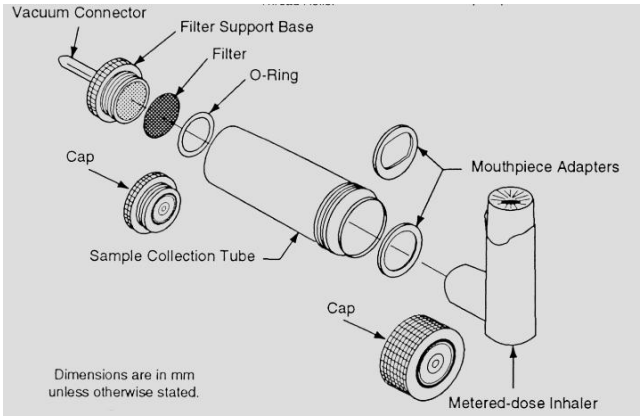

Figure 1. Dose collection apparatus for pressurised metered dose, as per Ph. Eur [12].

Table 1. Critical UoDD method parameters for MS and HS Sirdupla™ priming, dose collection and waste actuations

Parameter
Testing temperature
pMDI - Actuation force (waste only)
pMDI - Number of shake cycles / speed
pMDI - Depression hold time
pMDI - Post actuation delay (for next actuation)
pMDI - Post shake delay

The method life cycle management strategy is broadly summarised in Figure 2 [5]. The life cycle management tools (yellow boxes) supplement the traditional approach to method development/validation (blue boxes).

Initially, the pre-prepared generic versions of the Analytical Target Profile (ATP) and Risk Assessment (RA) for the methodology are reviewed, with any specific product considerations factored in. The generic assay ATP can be broadly described as 'Accurate, precise and robust quantification of the active substances over their specification range'. More specifically for this Sirdupla™ UoDD method, the ATP requirements were that the average dose was within 85 – 115 % of Seretide® Evohaler® label claim [15], with acceptable test variability (e.g. Relative Standard Deviation not more than 10%) for both Active Pharmaceutical Ingredients (API). It is imperative for generic products that there is this ATP prerequisite for accuracy. Such pre-defined objectives are peer reviewed and define the Method Development (MD) end point. The RA uses suitable risk management tools such as Fishbone diagrams, Cause & Effect matrices and Failure Mode Effect Analyses. These define appropriate controls and identify required MD and Method Validation (MV) experimentation, for each method variable, and are again peer-reviewed. MD/MV experimentation includes appropriate robustness / ruggedness studies to understand and control critical variables and define design space – as outlined in detail in this publication.

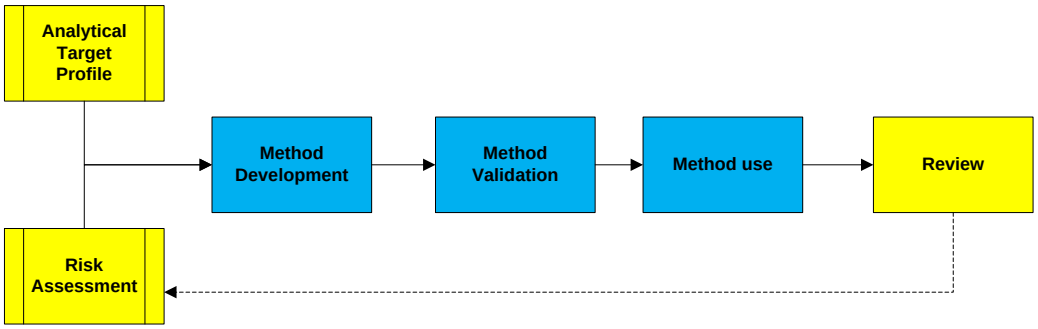

Figure 2. Summary of analytical method life cycle management strategy

Results and discussion

There are multiple variables which can influence UoDD data, as shown in Figure 3. Aside from the product related factors, risk assessments of the other variables are required. While some parameters have no impact if they are suitably controlled (e.g. cleaning), other more critical parameters require experimentation to determine their effects (e.g. shake / fire parameters for suspension pMDI's). Further risk assessments were required to determine the critical shake / fire parameters the experimentation would focus on.

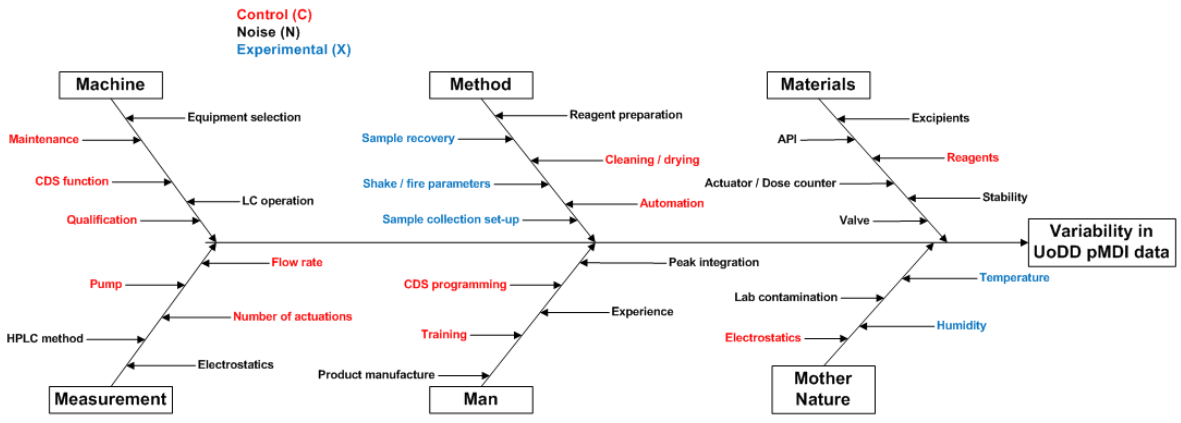

Figure 3. Fishbone diagram of sources of variability for UoDD data

Firstly, screening experiments were performed for the automated waste actuations to define appropriate settings for shake speed and depression hold time. Other high risk parameters were then assessed, particularly for their effects on container EOL data (See Figure 4).

Actuation force and post actuation delay were not found to be statistically significant in their effect on UoDD at EOL. A number of main effects were statistically significant - Temperature, number of shake cycles, and post-shake delay (Data in red). The settings for these parameters were optimised to minimise potential for through container life trends – e.g. sedimentation will be slower at a lower temperature with a reduced post shake delay.

As well as these statistically significant main effects, there are a number of statistically significant interactions present involving all five parameters, highlighting the importance of conducting experiments in a balanced design. As there are significant interactions involving actuation force and post actuation delay, which were not highlighted as significant main effects, these parameters are also appropriately controlled. It should be noted that no main effect or interaction was of large practical significance (All affect dose by less than 5%), demonstrating reasonable robustness over the entire experimental design space. In practice, a more constricted control space is applied for these parameters, which will therefore contribute significantly less than 5% to the overall test variability. All experiments on the waste actuations were performed with the MS Sirdupla™ product.

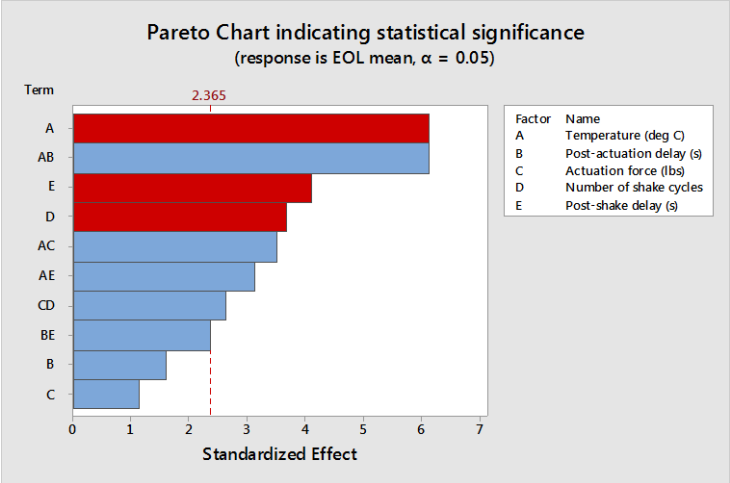

Figure 4. Pareto chart indicating statistical significance for MS Sirdupla™ FP UoDD data at EOL following waste actuations using the MDI FD-10 instrument (Any standardized effect >2.365 indicates a p value <0.05)

Next, a risk assessment was conducted to determine the shake / fire parameters to be assessed for the priming/collection actuations, performed manually by the analysts. Four parameters in total were chosen for experimentation. Screening experiments were performed using the HS product to define boundaries for optimisation studies with both product strengths. The screening experiments, and the subsequent optimisation tests, showed that shake speed and post actuation delay were not practically significant. Only depression hold time and post-shake delay were shown to be practically significant parameters, and are minimised to reduce sedimentation of the API and potential enrichment of the dose. As shown for the waste actuation studies, and for other products [16], post-shake delay is shown to be significant and requires tight control (See Figure 5). In practice, a zero second post shake delay cannot be achieved and we must consider the control that can be accomplished in a robust and rugged manner day after day by different analysts.

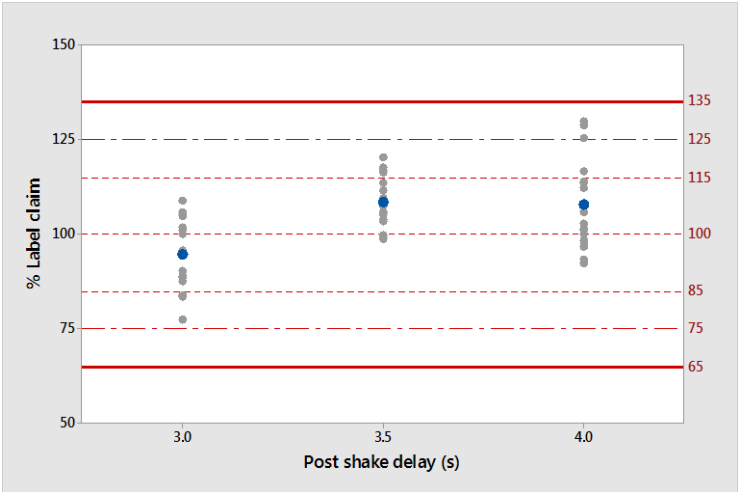

Figure 5. Plot of individual and mean MS and HS Sirdupla™ FP SOL data (% label claim) versus post shake delay

Lastly, control space settings were chosen from the experimental design space evaluated for both the waste actuations and the priming /collection actuations. These optimised settings were verified/validated as shown in Table 2.

The data generated were shown to be comparable with data generated for the Seretide® Evohaler® product. Data will continue to be assessed as part of the method review process in Figure 1, completing the life cycle loop.

Table 2. Method verification FP data (SOL/MOL/EOL) for Sirdupla™ versus Seretide® Evohaler®

Strength	Batch	% Label claim	
		Average	Standard Deviation
Sirdupla™ MS	1	93	6
Sirdupla™ MS	2	99	4
Seretide® Evohaler® MS	1	99	6
Sirdupla™ HS	1	102	7
Sirdupla™ HS	2	106	6
Seretide® Evohaler® HS	1	100	7

Conclusions

Analytical method development and validation was performed using a generic Quality by Design (QbD) framework for Life Cycle Management. Uniformity of delivered dose (UoDD) methodology was assessed using QbD tools such as risk assessments, an analytical target profile (ATP) and designed experiments to understand the performance of the Sirdupla™ generic product versus the Seretide® Evohaler® innovator product. Suitable control of the shake / fire parameters for priming, collection and waste actuations is critical for the analytical method. This is delivered via use of automation for the waste actuations only – automation could be extended to the priming/collection actuations, and even the sample recovery process, to exercise greater control. The optimised methodology demonstrates that the Sirdupla™ generic product generates comparable UoDD data to the Seretide® Evohaler® innovator product. This methodology is considered appropriate for the product lifespan, although will be subject to continuous improvement processes in line with the QbD paradigm.

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