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The Quality By Design (QbD) Sub-Team Of The European Pharmaceutical Aerosol Group (EPAG)

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Summary

This presentation gives an overview of the work to date and current activities of the Quality by Design sub-team. The team was formed in August 2006, with the scope of examining how Quality by Design might be practically applied to inhalation products using the principles outlined in ICH Q8 (Pharmaceutical development) (1) and ICH Q9 (Quality Risk Management) (2). A survey was conducted to elucidate the driving forces behind efforts to adopt QbD in the pharmaceutical industry and potential obstacles to its enactment. A model pMDI test case was established and a potential process for the application of QbD was examined. A further aim of the sub-team is to enter into dialogue and to work with the regulators to influence the evolution of QbD.

Introduction

The European Pharmaceutical Aerosol Group (EPAG) is a consortium of European Pharmaceutical Companies that develop new products for human use utilising the pulmonary or nasal routes of delivery. An EPAG sub-team was initiated in August 2006, with the goal of examining how Quality by Design (QbD) might be practically applied to inhalation.

The presentation gives an overview of the work to date and current activities of the Quality by Design sub-team, including an industry survey on drivers and obstacles to the implementation of QbD, an approach on practically applying QbD for a pressurised metered dose inhaler, and current thinking on the application of control space and design space concepts to the specifics of inhalation products when compared to conventional dosage forms.

Industry Survey

The QbD initiative was triggered back in August 2002 by FDA`s Pharmaceutical cGMPs for the 21st Century (3), subsequently supported by the PAT framework (4) as well as the principles outlined in ICH Q8 and Q9.
In October 2006, the EPAG QbD sub-team carried out a survey among the 19 EPAG member companies, to determine Industry's current drivers and potential barriers to the adoption of QbD for Inhalation Products

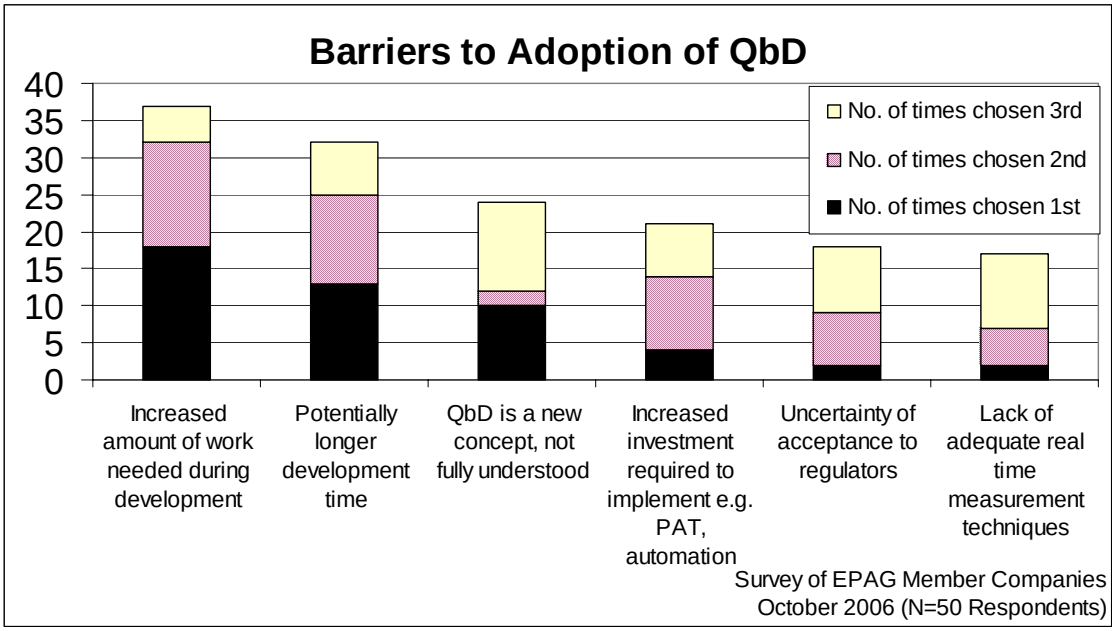
Drivers for QbD and Barriers to Adoption of QbD

The highest ranked responses were

1. "To gain improved product quality and understanding during development".
2. "To gain improved product quality of commercial products" (and hence a reduction in product recalls or product rejection at release).
3. "To reduce the need for post approval changes" i.e. to gaining increased regulatory flexibility.

The survey responses ranking the top 3 potential barriers to deployment of QbD are displayed in Figure 1. The highest ranked potential barrier was identified as "Increased amount of work needed during development", closely followed by "Potentially longer development time". The third highest potential barrier was "QbD is a new concept, not fully understood".

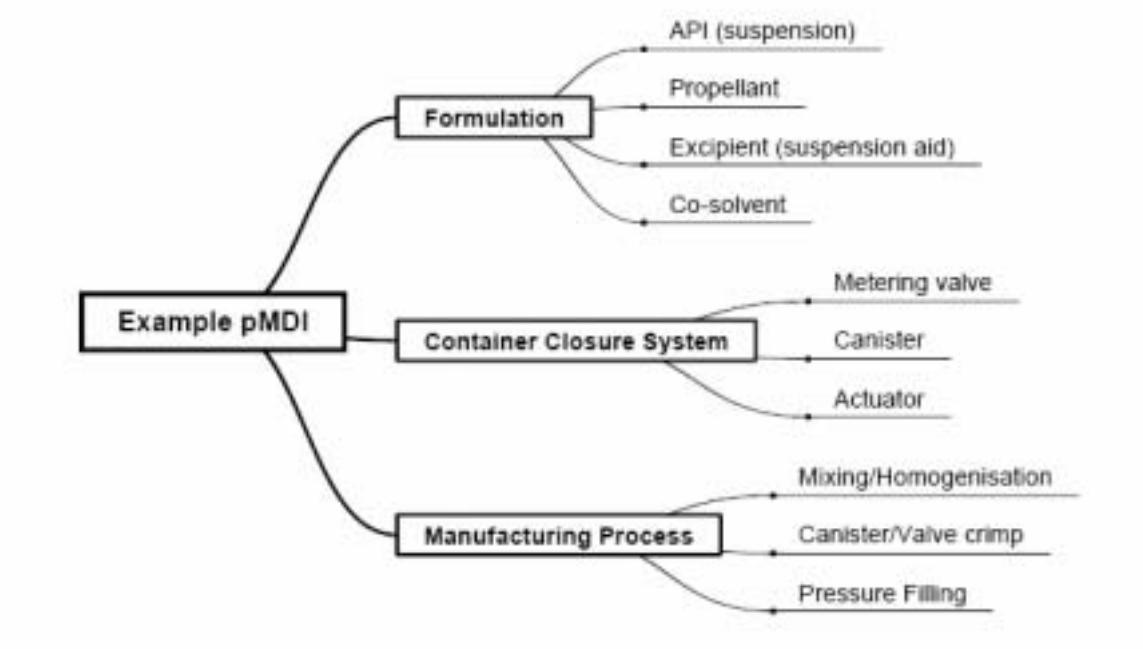
Figure 1: Barriers to Adoption of QbD



Application of QbD Principles to a Model pMDI Test Case

A model pMDI test case was developed as outlined in Figure 2:

Figure 2: Model pMDI System



The sub-team applied the following potential process steps for the application of QbD to a pMDI as the model system outlined in Figure 2:

1. **Determination of critical product performance characteristics** being related to in-vivo efficacy and safety
2. **Identification of potential material attributes and process parameters** which could affect the critical product performance characteristics i.e. those parameters which are the potential experimental variables in the design space. Parameters were brainstormed for the formulation, the container closure system and the manufacturing process
3. **Performance of a risk assessment of the potentially critical parameters** to identify those which are the critical quality attributes (CQAs), considering both the potential for direct effect and interactions. ICH

Q9 and ISO 14971 (Application of Risk Management to Medical Devices) (5) both describe systematic approaches for risk assessment and examples of tools for quality risk management. A simplified risk assessment based on collective knowledge of the aerosol delivery form was used to highlight key variables.

4. **Performance of screening and design space experiments to establish the design space** and explore the impact of individual parameters and their interactions setting their appropriate ranges and relative importance. Careful consideration of the types of experimental design (e.g. discrete DoEs vs. full factorial designs), the number of replicates and repeat runs and the capability of the analytical test methods is required to ensure adequate statistical power as a basis for informed and correct decisions while keeping experimental cost and efforts manageable.
5. **Determination of the control space and relation to the design space,** defining the established range over which the critical formulation attributes, critical container closure attributes and critical process parameters have been demonstrated to produce product with acceptable performance i.e. provide assurance of quality, considering also the appropriate manufacturing scale and scaleability of results.

Questions and current thinking on the application of control space and design space concepts

The test case revealed several aspects relating to the use of design space versus control space. The sub-team is addressing a number of questions, such as:

- Should the batches of product to be used to establish the product performance characteristics and the product stability performance be manufactured from the wider design space or from the control space?
- Should the batches of product for phase III clinical studies be manufactured from the wider design space or from the control space?
- Will risk assessment be adequate to justify a post approval change within an established design space or would the change need to be “validated” through manufacture of commercial scale batches?
- How will QbD impact the analytical testing methodologies required to measure design space responses?
- What is it that makes application of Quality by Design more complex for inhaled products compared to other dosage forms?

Test methodologies in a QbD environment

The justification of design spaces for formulation, process and device is for many attributes based on product performance testing. Available compendial methods for delivered dose and aerodynamic particle size distribution are generally considered to be of low efficiency, i.e. the quality information output per effort is in most cases low. This aspect is of considerable importance also for QC control testing of inhalation products. To increase the product knowledge during development the group would like to explore the possibility to develop alternative, efficient analytical methods (e.g. short stack impactors, optical instruments etc.). Such methods could be used once the basic understanding of product performance, and a link between the compendial method and alternative method, has been established. One of the identified barriers towards the implementation of QbD (see industry survey above) is the lack of adequate real time measurement techniques which can be applied during product manufacture (i.e. prior to filling the formulation into the device) to predict product performance for inhalation products. Identification of such methods and establishing their regulatory acceptance is therefore also of interest to the sub-team.

What is it that makes application of quality by design more complex for inhaled products compared to other dosage forms?

The development, registration and routine manufacture of inhalation products is understood to be more complex, and therefore more challenging (requiring greater time and expense), than ‘standard’ dosage forms such as solid oral dosage applications. It is probable that this added complexity will also create challenges for the application of QbD. In order to understand challenges for the application of QbD the sub-team has begun to identify areas that distinguish inhalation product manufacture from more standard processes, and the impact of these areas on a QbD approach.

The areas identified by the sub-team can be grouped under the following six headings:

	Areas of Distinction
1	Inhalation manufacturing often exhibits low process capability
2	The final product is a device in association with a formulation
3	Product handling may affect received dose
4	Environmental effects may influence product manufacture and use
5	Low testing efficiency of aerodynamic particle assessment methods
6	Lack of clear *in vitro - in vivo* correlations

(It was noted that these concerns are not all applicable to all inhalation products, but were generally well recognised.)

Two areas of particular concern were identified that will challenge the inhalation industry when applying QbD to inhalation products:

1. Low testing efficiency of aerodynamic particle assessment methods, especially ACI and NGI.
   Challenge 1: *Can the industry develop methods that are quicker and less variable (and cost effective)?*
2. Lack of clear *in vitro - in vivo* correlations, particularly for locally acting products.
   Challenge 2: *Can the analytical experts develop in vitro methods that give better correlation with in vivo testing?*
   Challenge 3: *Can the clinical experts develop better discriminating in vivo testing models that require smaller sample sizes to enable more clinical testing of more process/formulation variants in supporting the development of a design space?*

CONCLUSIONS

Drivers for the adoption of QbD within industry are primarily associated with the development of enhanced product understanding. The benefits of the deployment of QbD are seen to outweigh the barriers i.e. the additional work and time that may be required during development. Integration of PAT measurements, rapid/automated laboratory testing and scalable laboratory scale manufacturing methods are all elements which will help lessen the barriers and facilitate the move to QbD The EPAG QbD sub-team used a test case for one class of inhaler as a way of developing a road map for using a QbD approach that will assist in its implementation.

The steps outlined in the road map are generally applicable to any type of dosage form; however the complexity at each stage is likely to be elevated for inhalation products. The potential for interaction between the formulation and the delivery device may well complicate the experimental design and interpretation of data. Additionally, the labour intensity of current methods for particle size distribution, arguably the most critical product performance characteristic, will no doubt increase the burden of testing. Hence, it is the focus of the sub-team to identify what makes the application of Quality by Design more complex for inhaled products.

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