APPLICATION OF QUALITY BY DESIGN TO INHALATION PRODUCTS

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SUMMARY

This paper describes the driving forces behind efforts to adopt QbD in the pharmaceutical industry. Industry surveys have shown that the primary reasons for adopting QbD are to improve product quality and understanding while the increased workload associated with the effort was cited as the greatest obstacle to its enactment. The paper also describe the steps necessary to gain approval for freedom of operation within design and/or control spaces for a theoretical pMDI that has been developed in accord with the principles of QbD.

INTRODUCTION

The European Pharmaceutical Aerosol Group (EPAG) is a voluntary non-profit making consortium of European Pharmaceutical Companies that develop new products for human use utilising the pulmonary or nasal routes of delivery. One of the objectives of EPAG is to share scientifically-based best practice. 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 products using the principles outlined in ICH Q8, Pharmaceutical Development (1) and ICH Q9, Quality Risk Management (2).

The first part of this paper discusses the drivers within industry for adoption of QbD and the barriers to adoption, determined from an industry survey within the EPAG member companies. The second part sets out an approach on how one might practically apply QbD as exemplified for a pressurised metered dose inhaler.

WHAT ARE THE INDUSTRY DRIVERS AND BARRIERS FOR ADOPTION OF QbD?

Industry Survey

The QbD initiative has given the pharmaceutical industry the opportunity to modernise its approach to product development. Investment in acquiring and developing knowledge of product characteristics and manufacturing processes can lead towards quality being designed into products and away from quality assurance through end-product testing; it creates a basis for flexible regulatory approaches. This shift in paradigm was triggered back in August 2002 when the FDA outlined its initiative on Pharmaceutical cGMPs for the 21st Century (3). Subsequent guidance under the PAT framework (4) as well as the principles outlined in ICH Q8 and Q9 have further supported the move to make "Quality by Design" a reality.

In October 2006, the EPAG QbD sub-team carried out a survey among the nineteen EPAG member companies that were working on both drug products and devices, to determine Industry's current answers to the questions: "What are the drivers for adoption of QbD for Inhalation Products?" and "What are the potential barriers to deployment?"

Drivers for QbD

Respondents were asked to select the top 3 drivers for deployment within their companies in order of importance. The survey responses are displayed in Figure 1. The highest ranked response was "To gain improved product quality and understanding during development" with 26 of the 51 respondents selecting this as their top reason and 40 of the 51 respondents selecting this in their top 3. The second highest response was "To gain improved product quality of commercial products" (and hence a reduction in product recalls or product rejection at release). The third highest reason given was "To reduce the need for post approval changes" i.e., to gaining increased regulatory flexibility. This option was selected as the primary driver for QbD by 4 of the 51 respondents.

Barriers to Adoption of QbD

Respondents were asked to rank the top 3 potential barriers to deployment of QbD within their companies, in order of importance. The survey responses are displayed in Figure 2. The highest ranked potential barrier was identified as "Increased amount of work needed during development"

with 18 of the 50 respondents selecting this option as their top choice and 37 selecting this option in their top 3 choices. This was closely followed by "Potentially longer development time". The third highest potential barrier was "QbD is a new concept, not fully understood" with 10 respondents selecting this as their primary concern.

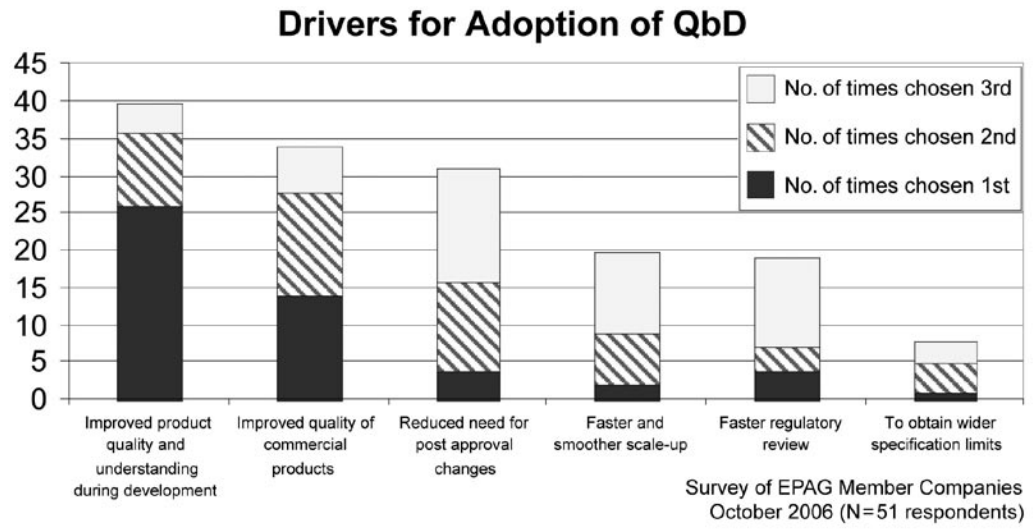

Figure 1. Drivers for Adoption of QbD.

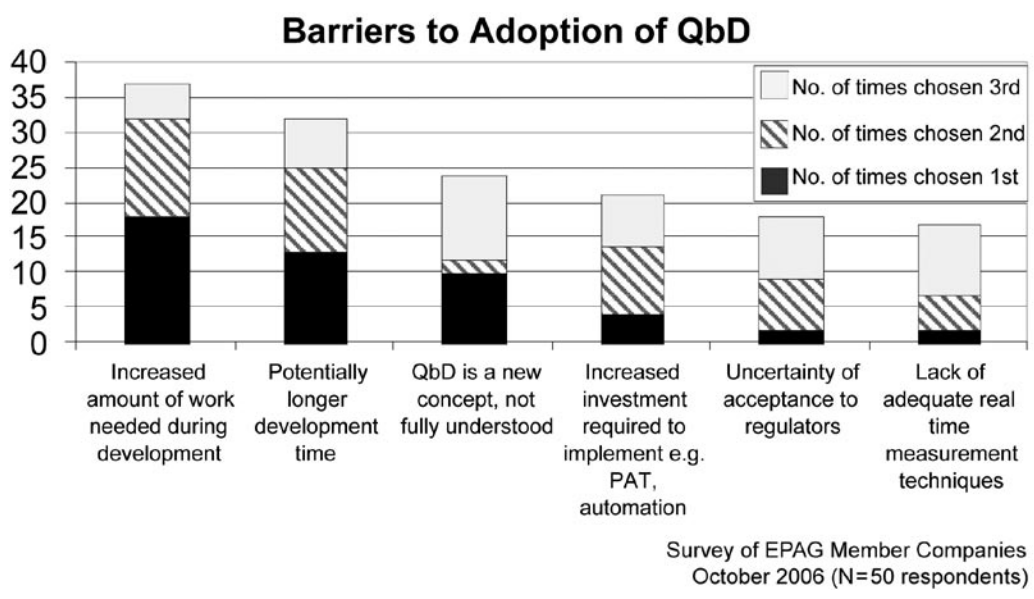

Figure 2. Barriers to Adoption of QbD.

APPLICATION OF QBD PRINCIPLES; A TEST CASE

The sub-team developed a road-map identifying how QbD may be applied to a hypothetical test case. The steps identified by the sub-team are summarised in Figure 3. The considerations at each stage are discussed below.

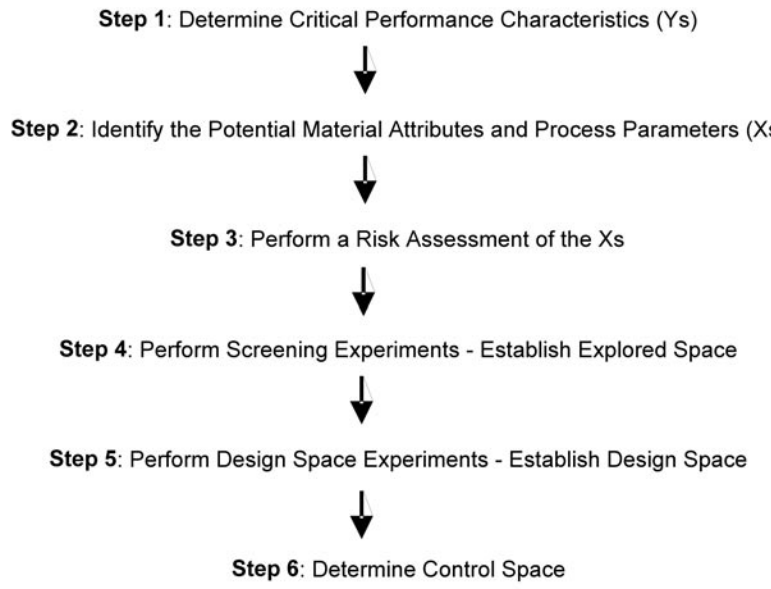

Figure 3. **Application of QbD – Process Steps [Ys represent experimental responses or measurements and Xs represent experimental variables].**

Selection of Model System

The sub-team selected a pressurised metered dose inhaler (pMDI) as the model system with which to work through a theoretical exercise applying the QbD paradigm. The pMDI system was defined as shown in Figure 4.

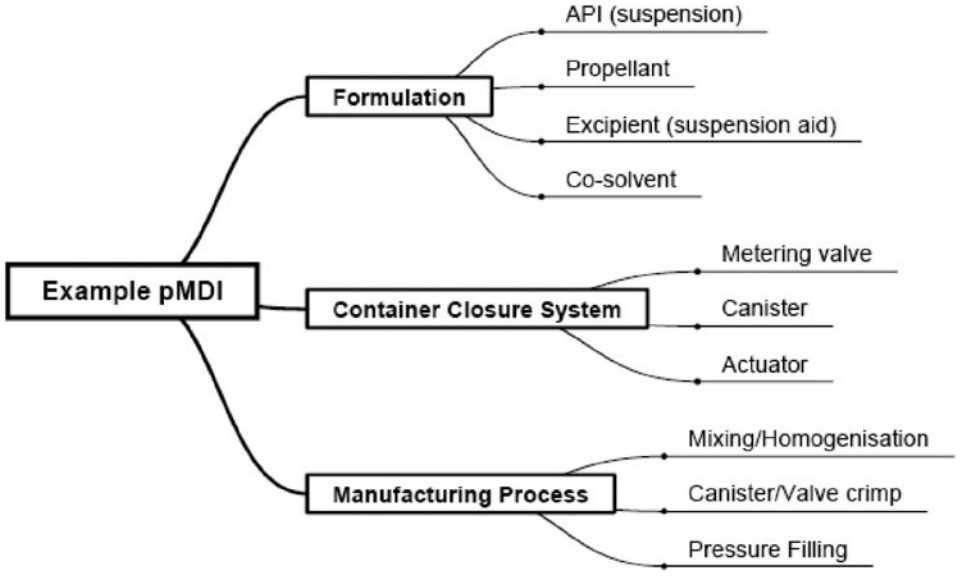

Figure 4. **Model pMDI System.**

- Suspension formulation containing a single active pharmaceutical ingredient (API) in propellant containing a co-solvent and an excipient to aid suspension.
- Container Closure System (CCS) consisting of a standard retention metering valve, uncoated canister and plastic actuator
- Manufacturing process employing single stage pressure filling through the valve.

For the sake of simplicity, the need to also consider the quality attributes associated with additional items such as dose counters and spacers has been ignored in this paper.

Critical Product Performance Characteristics (Ys)

The **first step** is to determine the critical product performance characteristics i.e., the responses (Ys) to be used for the design space. For inhalation products, as with any other pharmaceutical product, these characteristics are related to in-vivo efficacy and safety; efficacy traditionally being indicated in-vitro through the magnitude of the delivered dose and particle size distribution/fine particle fraction, safety being assessed in-vitro through levels of impurities associated with both the formulation (degradation products) and the container closure system (leachables, foreign particulates).

The Variables (Xs): Material Attributes and Process Parameters

The **second step** is to identify the material attributes and process parameters which could affect the critical product performance characteristics i.e., those parameters which are the potential experimental variables (Xs) in the design space. In the sub-team test case the parameters were brainstormed in three areas; the formulation, the container closure system and the manufacturing process. Figure 5 displays the output for the formulation assessment, as an example.

Risk Assessment

Step 3 is to perform a risk assessment of the potential 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. Whichever approach is applied, it is important to note that this assessment will be heavily reliant on available information and experience and would need to be performed on a case-by-case basis. In the sub-team test case a simplified risk assessment based on collective knowledge of the aerosol delivery form was used to highlight key variables. In this hypothetical test case **seven potential critical quality attributes** were identified as follows:

- Formulation – *API particle size, excipient %w/w, co-solvent %w/w*
- Container closure system – *actuator orifice diameter, actuator orifice length*
- Manufacturing process – *homogenisation speed, homogenisation time*

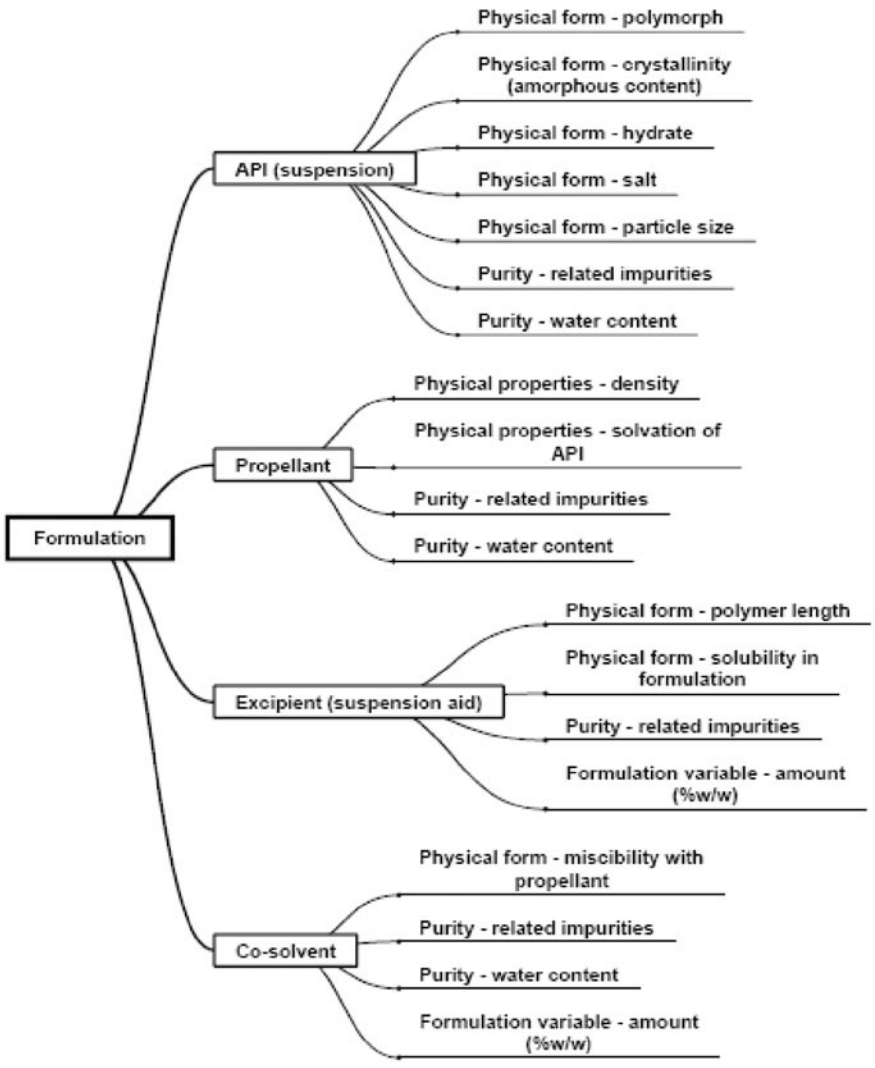

Figure 5. Potential Formulation Parameters.

Experimental Strategy to Define the Design Space

Step 4 is to perform **screening experiments** (to establish the explored space), primarily to establish the impact of individual parameters and their interactions. Different types of design may be used, the choice of which will be dependent on the parameters to be explored; the list therefore will be product specific. When considering the ranges of the parameters to be explored, then these should be wider than the range which is anticipated to result in acceptable product performance, to allow the design space to be defined within the explored space.

Equally important to the final experimental design is the consideration of the number of replicates for each experimental run and the number of repeat test measurements to be made. Careful consideration of the likely impact of batch to batch variability, and the capability of the analytical test methods in light of acceptable specification ranges as well as the anticipated spread of data for the critical responses, is required to ensure that adequate statistical power is available to make informed and correct decisions based on the collected data.

A further consideration is whether any of the parameters being investigated are likely to affect the stability of the product and hence whether product performance will need to be assessed over time, as a distinct and separate part of the overall experimental design.

The data generated during this screening phase should determine which of the parameters to investigate as part of the design space and their appropriate ranges, as well as the most appropriate type of design to use.

In the sub-team example, the seven critical quality attributes from the risk assessment (Step 3; italics) were considered in the screening experimental design. Ideally from the perspective of product and process understanding, all seven factors would be taken into a single design of experiments (DoE). A single, half factorial design of experiments, assuming 2 levels for each factor and 3 centre points would require 67 runs and hence would be very costly to run. Reducing the resolution of the design down to a one eight factorial with centre points would require 19 runs, however the trade off in this reduced design is the increased potential for information on interactions to be confounded. An alternative approach that was considered was to run a number of discrete DoEs, for example for the formulation parameters, container closure parameters and manufacturing process parameters respectively. Such an approach is likely to be practically easier to manage. In addition it would be less costly to repeat one of the discrete DoEs if needed e.g., if the ranges selected are found not to be appropriate. The disadvantage of using several discrete DoEs is that this approach will give less information on interactions between the parameters. Take for example the potential situation where the effect of the % co-solvent in a product and the effect of actuator orifice diameter in the container closure system on the fine particle fraction do not behave additively and these parameters have been investigated in separate DoEs, then their true impact on the overall product performance will not be predicted from the experimental design.

The sub-team also assessed the number of replicate measurements that would be required for each response and each DoE run. Taking the example of fine particle fraction assessment and assuming an overall Relative Standard Deviation (RSD) of 5% for this type of method, eight replicate measurements would be required to give a 95% confidence of detecting a difference of 10% between design points.

Step 5 is to establish the **design space**. The output from the screening experiments should identify those parameters having the greatest influence on product quality attributes (Ys) and the ranges over which they are predicted to give product with acceptable performance; this information will determine the framework for the design space experiments. In addition to the DoE strategy and number of replicates, consideration should be also be given to the appropriate manufacturing scale on which to perform the design space experiments. For example, if performed at laboratory scale or pilot scale, how representative will the DoE data be for the commercial manufacturing process?

Interpretation of Results and Control Space

The primary output from the design space experiments should be a definition of 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.

In addition, the output from the design space DoE will be a matrix of equations describing each of the critical response factors (Ys) as a function of the material attributes and process parameters (Xs). For a DoE based on two parameters (Xs) then this can be easily depicted as a contour plot or 3-D response surface for each response. However once further (>2) factors become

important (a likely result in this case, where 7 variables have been identified), then visualisation of the design space becomes much more difficult. In practice, it is recognised that this type of multivariate statistical analysis not only requires appropriate expertise and software, it also imposes unique challenges to those who wish to present and discuss the results and their implementation. Recognition also needs to be given to the fact that the experimental responses may be expressed as mean values with associated uncertainty (e.g., 95% confidence intervals), whereas product specifications may well be expressed in terms on individual values

One approach which could be applied to refine the model is to perform a sensitivity analysis i.e., to model the predicted change in each of the responses (Ys) as each of the parameters (Xs) are varied within the design space limits. The output from this analysis could be to establish the relative importance of each parameter and hence focus on the major variables when establishing the control space.

Questions Remaining to be Addressed

One of the elements being advocated in the new paradigm of QbD is that it can create a basis for increased "regulatory flexibility". ICH Q8 states that for companies that establish product performance over a wider range of material attributes and process parameters i.e., establish a design space which is broader than the control space, then the opportunity exists to develop regulatory flexibility. For example, it may be possible to make manufacturing process improvements within the approved design space without further regulatory review.

Having worked through the hypothetical test case and the steps outlined above the subteam still have identified several unanswered questions that relate to this topic and the use of design space versus control space. Some of these are listed below:

- Should the batches of product to be used to establish the product performance characteristics in the development pharmaceutics studies and the product stability performance for product registration be manufactured from the wider design space or from the control space?
- Should the batches of product which will be in the phase III clinical studies be manufactured from the wider design space or from the control space?
- If the design space has been established using pilot scale batches and then a company wants to make a process improvement within the design space post approval, is a risk assessment for the change adequate or would the change need to be "validated" through manufacture of commercial scale batches?

Addressing these questions, and others, is currently the focus the activities within the EPAG QbD sub-team.

CONCLUSIONS

Drivers for the adoption of QbD within industry are primarily associated with the development of enhanced product understanding. To move to the new paradigm forward, the benefits need to been 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 has began to work on a model 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. The labor intensity of current methods for particle size distribution, arguably the most critical product performance characteristic, will no doubt increase the burden of testing. Hence, although it is possible to adopt QbD for inhalation products, the hurdles of development resource and time to deliver are currently higher than exist for other dosage forms.

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