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Application of Quality by Design Principles for the Definition of a Robust Crystallization Process for Casopitant Mesylate

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Abstract:

GlaxoSmithKline (GSK) has identified casopitant as a potent NK_1 antagonist. It was selected for its potential activities on a number of therapeutic targets such as inflammatory bowel disease, overactive bladder, CNS disorders and others. The mesylate salt of casopitant was selected for full development using a quality by design (QbD) approach in which a control strategy was developed from a design space, underpinned by process understanding and risk analysis for an enhanced level of quality assurance. As the concepts of design space and control strategy in the QbD framework move on from their inception to implementation, the ambiguity of definition has led to considerable discussion, diversity of opinions and uncertainty around how best to define these ideas. This contribution provides an outline of the sequential experimentation and analyses that led to the construction of a Bayesian approach to the ICH Q8 definition of Design Space. This uses a predictive approach for multiple response surface optimisation to identify a region of process operating conditions where all quality attributes of the active pharmaceutical ingredient (API) are likely to meet specifications with a high degree of confidence. Boundaries of assurance for design space and control strategy are introduced that provide a basis for defining dynamic operating ranges that should enhance the scope of operation and manufacturing flexibility that the regulatory agencies are encouraging. This new paradigm provides an opportunity to move away from the traditional concept of documenting static normal operating ranges (NOR) and proven acceptable ranges (PAR) univariately in a table or providing them as a list to regulators as part of regulatory submissions. While the latter approach is practical for documentation and serves as a simple instruction to manufacturing as to where a process should be allowed to run, it is not ideally suitable for describing a multidimensional design space. Model/parameter-based control is discussed through a worked example on the casopitant crystallisation step of a particle-forming routine.

1. Introduction

Quality by design (QbD) forms an integral part of an industry-wide desire to improve drug product manufacture. QbD is a product design philosophy where processes are developed which have a high level of assurance of producing product of sufficiently high quality. Quality is designed into the process by understanding the relationship between input attributes, process parameters and the quality characteristics of the final product. This knowledge contributes to establishing a control strategy in order to consistently produce product of the desired quality. This will include control of input attributes and process parameters and may involve feed-forward and feed-back mechanisms.[1a]

This new paradigm to process development has been described in a number of regulatory guidelines (ICH Q8, ICH Q9 and ICH Q10)[1] that have been issued. In particular, these guidelines focus their attention on different aspects of QbD. For example, ICH Q9[1c] describes the risk management tools that can be used to successfully manage risk, whereas ICH Q10[1d] has introduced the concept of a control strategy defined as a set of controls from current product and process understanding that assures process performance and product quality.

ICH Q8[1b] is geared towards the definition and implementation of "Design Space" (DS). This document defines DS as "the multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality". It states further that: "Working within the DS is not considered as a change. Movement out of the DS is considered to be a change and would normally initiate a regulatory post approval change process. DS is proposed by the applicant and is subject to regulatory assessment and approval". The creation of a DS for a manufacturing process offers an opportunity not only to make changes within the DS without regulatory approval, but also provides openings for additional experimentation after regulatory approval of the manufacturing process that can aid in further improvement.

This paper outlines principles of a QbD approach applied to the development of the crystallization step (stage 2d) for the drug substance manufacturing process of casopitant mesylate **1** (Scheme 1), a potential drug active in inflammatory bowel disease, overactive bladder, CNS disorders and others. The novelty features of this article comprise methodology and implementation strategy in defining design space and thereafter

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(1) (a) A glossary section with definitions of terms used within this text is included in Appendix 1. (b) *ICH Q8 Pharmaceutical Development*, (R2); U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER): Rockville, MD, Aug 2009. (c) *ICH Q9 Quality Risk Management*; U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER): Rockville, MD, June 2006. (d) *ICH Q10 Pharmaceutical Quality System*; U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER): Rockville, MD, April 2009.

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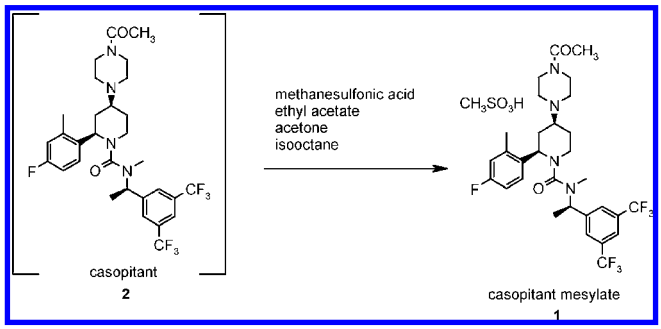
Scheme 1. **Final crystallization to casopitant mesylate**



executing the control strategy in the form of a batch record that an operator can follow.

In sections 2 and 3, the article begins by describing the crystallisation process and the elicitation of drug substance Critical Quality Attributes (CQAs) impacting this process (crystalline form and casopitant impurities). Section 4 gives an early insight into the crystallization development and solvent selection activities undertaken in deriving the composition there from. The Parameter Attribute Matrix (PAM) and Risk Assessment tools are initiated as a precursor to identifying potential parameters and/or attributes which may interact and impact product quality in Section 5. Section 6 lays out the sequential experimentation that was conducted in identifying and understanding these interactions.

The pitfalls of the commonly used "Overlapping Mean Responses" (OMR) approach for defining Design Spaces from derived empirical models is discussed in section 7 as well as introducing the alternative Bayesian predictive approach. This latter approach not only takes into account the random variability in the process, uncertainty in the parameter estimates and the correlations between the (CQAs) at fixed operating conditions, it also allows to address the key issue of quantifying the level of assurance at **no extra experimental cost** which is core to the ICH Q8, Q9 and Q10 guidance documents. Bayesian statistical analysis is well suited for constructing predictive models associated with scientific processes. As such, it is finding a variety of applications in the chemical and pharmaceutical industries.[2] Readers new to Bayesian data analysis may wish to consult one of the many textbooks in this area, such as the recent one by Christensen et al. (2010).[3]

We conclude the paper by supporting an innovative approach for navigating through the design space using dynamic flexible ranges seen as a way of moving the industry tradition of static normal operating ranges (NOR) and proven acceptable ranges (PARs) prevalent in historic regulatory submissions.

2. Final Crystallization Process

The commercial process to synthesise casopitant mesylate is described in a previous paper.[4] In the final crystallization step, casopitant mesylate **1** (Scheme 1) is obtained via a seeded reactive crystallization where methanesulfonic acid is added to casopitant **2** in an ethyl acetate, acetone and isooctane mixture. The work carried out to select and optimise the particle forming step is described in this article.

In order to deliver the drug substance with consistent properties, extensive process understanding and optimisation studies were undertaken. The experimental conditions were consequently changed during the course of the development of the process. In particular, during the preclinical and clinical studies, the particle forming step solvent was altered twice, initially using ethyl acetate and later to the aforementioned mixture. The relative ratio of these three solvents was finally optimized before finalising the commercial process.

3. Drug Substance CQAs Impacted by the Crystallization Process

The drug substance critical quality attributes (CQAs) of note in the definition of the control strategy (ICH Q10) consisted of attributes of both the crystalline form and the casopitant impurities. An important attribute also considered in this investigation was the particle size distribution (PSD) of the drug substance. Casopitant mesylate is a soluble molecule (BCS class I/IIa dose related) that is formulated by wet granulation in a high-shear mixer. This particle agglomeration process is extensively used in the pharmaceutical industry. Particle size enlargement is attained by the addition of a liquid to the powder or a mixture of powders that are being mixed in a high-shear mixer. The resulting particles, termed granules, usually have larger particle size and bulk density compared with those of the starting material. Properties of the starting material such as particle size can affect strength and deformability of moist granules and hence their behaviour in the high-shear granulator at both the nucleation and coalescence stages. Ranges of particles of casopitant mesylate powders (D90 ranging from 15 to 60 μm) have been submitted to this formulation process with success, the resulting drug product always meeting specifications.

On the basis of this experimental data, the PSD was not identified as a drug substance CQA but was included as one of the responses of the multivariate study for which to obtain further confirmation. Where appropriate, a number of other physical properties were measured and evaluated against typical values or acceptance criteria when available.

3.1. Crystalline Form. Crystalline form was a drug substance CQA for casopitant mesylate. Investigations demonstrated that it was a combination of two crystalline forms, Form 1 predominantly and Form 3 present up to 27% w/w. The control of the crystalline form in the manufacturing process was operated via the synthetic procedure. Form 3 and its controls in the drug substance are described in another article.[5]

3.2. Casopitant Impurities. The drug substance CQAs in the context of stage 2d were those impurities having the potential to contaminate the drug substance. They are the stereoisomers of the casopitant (Scheme 2) and the impurities arising from the contaminants of the starting material 1-acetylpip-

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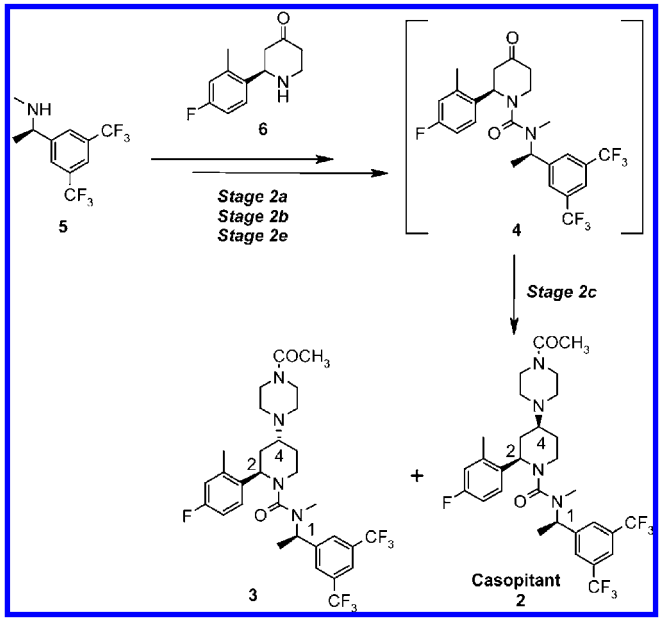
(3) Christensen, R.; Johnson, W.; Branscum, A.; Hanson, T. E. *Bayesian Ideas and Data Analysis: An Introduction for Scientists and Statisticians*; CRC Press: Boca Raton, FL, 2010.
(4) Cimarosti, Z.; Bravo, F.; Castoldi, D.; Tinazzi, F.; Provera, S.; Perboni, A.; Papini, D.; Westerduin, P. *Org. Process Res. Dev.* **2010**, *14*, 805.
(5) Cimarosti, Z.; Castagnoli, C.; Rossetti, M.; Scarati, M.; Day, C.; Johnson, B.; Westerduin, P. *Org. Process Res. Dev.* DOI: 10.1021/op100150b.

Scheme 2. **Formation of casopitant stereoisomers**



Scheme 3. **Drug substance CQAs from 1-acetylpiperazine impurities**

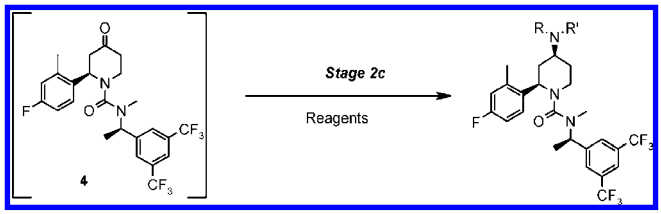


Table 1. **Formation of casopitant stereoisomers**

Amine	Piperidone	Casopitant stereoisomers*
(*S*)-**7**	(*S*)-**8**	(1S,2S,4R)-**9** and (1S,2S,4S)-**10**
(*R*)-**5**	(*S*)-**8**	(1R,2S,4S)-**11** and (1R,2S,4R)-**12**
(*S*)-**7**	(*R*)-**6**	(1S,2R,4R)-**13** and (1S,2R,4S)-**14**

* The configuration of the stereocenters according to Scheme 2 is reported.

erazine (Scheme 3 and Table 2). The rationale for their formation has been reported in a previous paper[2] and summarized in the next sections.

3.2.1. Casopitant Stereoisomers. The formation of stereoisomers of casopitant is described in Scheme 2.

Table 2. **Structures of the 1-acetylpiperazine impurities**

Reagents	NRR'	Compound Number
HCOOH,		**15**
		16
		17

The same synthetic path was also pursued by the enantiomers of the compounds (*R*)-amine **5** and (*R*)-piperidone **6**, (*S*)-amine **7** and (*S*)-piperidone **8**, respectively (Scheme 2), leading to the formation of the other casopitant stereoisomers as detailed in Table 1.

It is worth noting that the compounds belonging to the following pairs **3**−**10**, **11**−**13**, **12**−**14** and casopitant-**9** are enantiomers.

3.2.2. Acetylpiperazine Related Impurities. Process understanding studies also highlighted that one of the reagents, 1-acetylpiperazine may contain piperazine, 1-propanoylpiperazine, and *N*-(2-aminoethyl)acetamide as impurities. It was noticed that these impurities reacted in the stage 2c chemistry (Scheme 3) by generating three impurities with the possibility of contaminating the drug substance (compounds **15**, **16**, and **17**, see Table 2). These potential impurities were defined API CQAs, and their specification limits are reported in Table 3.

At the time of the study, suitable specification limits for the precursors of these drug substance CQAs were defined; the rationale in support of their levels is reported in a previous paper.[2] A summary is presented in Table 3.

Of further note, the effect of the casopitant free base impurity profile on the stage 2d output was investigated using three different batches with varying levels of purity: a standard purity batch, a customised purity batch, and a mid-purity batch obtained by mixing the previous two batches (labelled as +1, −1, and 0 in future sections). The customised purity batch was prepared by artificially doping high levels of impurities into a solution of casopitant free base at or above the specification limits. Of further note is that the impurity profile of casopitant is, in principle, an attribute that results from the optimized chemical transformations. Nevertheless, in this contribution it has been considered as the starting material of the final drug substance crystallization and, as a result, a process parameter that can affect the outcome of the final crystallization.

4. Process Design: Early Crystallization Development and Solvent Selection

The definition of the crystallization process of the drug substance was the result of an integrated set of contributions

Table 3. **Summary of the specification limits for drug substance precursors**

impurity	level of impurity (% a/a)	drug substance CQA impacted[a]	specification limit drug substance CQA in the drug substance (% w/w)
(*S*)-piperidone **8** in (*R*)-piperidone **6**	1.5	**11**−**13**	NGT 0.4
		12−**14**	NGT 0.1
		3−**10**	NGT 0.6
		9	NGT 0.15
(*S*)-amine **12** in (*R*)-amine **5**	0.7		
piperazine in 1-acetylpiperazine	0.3	**15**	NGT 0.3
1-propionylpiperazine in 1-acetylpiperazine	0.1	**16**	NGT 0.15
N-(2-aminoethyl)acetamide in 1-acetylpiperazine	0.15	**17**	NGT 0.15

[a] The casopitant stereoisomers **11**−**13**, **12**−**14**, and **3**−**10** are reported together as the analytical method was not chiral. **9** is the casopitant enantiomer, and a chiral method was used for its detection.

which encompassed, amongst others, particle sciences, chemical route development, physicochemical properties, and formulation. As a result of a salt screen activity, the mesylate version was selected as the preferred version prior to the start of the clinical program. This salt can be directly crystallized at the end of the last chemical transformation from the crude mixture. However, considering the complexity of the composition of this crude mixture, it was crucial to select the right process parameters and, in particular, the right solvent composition.

In the crude mixture resulting from the last chemical transformation workup (stage 2c), the casopitant free base was dissolved in ethyl acetate. The solubility of the free base in ethyl acetate was high and was increased by the presence of impurities as well. On the other hand, as a mesylate salt, the solubility of the drug in ethyl acetate was very low. For this reason it was important to identify a solvent system where the degree of supersaturation during the reactive crystallization could be tightly controlled. Amongst the evaluated solvents, through solvent screening activities, acetone was found to be the most promising one. The crystallization was finally completed by the addition of a genuine antisolvent such as isooctane.

4.1. Study 1. An initial three-mixture component experimental design of 16 runs was run across a constrained region on a 50-mL reactor equipped with mechanical stirring and turbidity probes. Composition mixtures included acetone, ethyl acetate, and isooctane with the following responses considered:

(i) purity evaluated in terms of casopitant mesylate assay by HPLC and impurity profile by HPLC and NMR
(ii) solid recovery
(iii) particle size distribution
(iv) habit and particle aggregation by polarized light microscopy
(v) form

The total solvent crystallization volume was limited to 10 volumes, a constraint driven by the manufacturing equipment and by project needs.

From the outcome summary, it was inferred that the purity profile of the isolated API was well within the limit of specifications set for this drug. Just at very high antisolvent content, when acetone amount is kept low, precipitation of the unwanted anti isomer (compound **3** in Scheme 2) was observed. The solid recovery was strongly influenced by the amount of acetone present in the mixture; high recovery being obtained when acetone was low. Ethyl acetate and isooctane act as antisolvents and contribute to the increased solid recovery.

Table 4. **Factor levels for the process/mixture design**

factors	low	high
acetone (vol)[a]	4.3	5.7
ethyl acetate (vol)	1.6	3.0
isooctane (vol)	2.7	4.1
temperature (°C)	35	45

[a] Volumes in the table are referred to 0.86 wt % of casopitant **2**.

The habit of the isolated API was platelike in all the reported experiments. The particle size distribution was affected by the acetone percentage in the solvent mixture with respect to isooctane and ethyl acetate.

4.2. Study 2. A follow-up combination process/mixture design was run to hone in on the region of interest with temperature at the point of seeding and during the addition of isooctane incorporated into the design. The solvent composition mixture and temperatures ranges considered are given in Table 4.

The same responses as in the previous study were evaluated. The API specifications were always met in the evaluated experimental design with solid recovery always greater than 90% wt/wt. Habit and particle association were evaluated by optical microscopy. In particular, platelike habit was observed in all the samples. Agglomeration was important mainly at 35 °C especially at relatively low amounts of acetone. The particle size distribution measured was influenced by solvent composition and temperature. Generally, the smallest particles were obtained at low acetone amount and high ethyl acetate and isooctane volumes.

These initial small-scale studies served as a basis for understanding the definition of the crystallization process. In particular, considering the relative complexity of the solvent systems, the reported results were useful in getting an initial evaluation of the potential quality critical process parameters (potential QCPPs) that may have affected the API attributes.

5. Parameter Attribute Matrix and Risk Assessement

The process of defining the design space and control strategy was initiated by brainstorming a parameter attribute matrix (PAM) where each parameter identified was assessed by the risk it imposed on the drug substance CQA. This activity identified the process parameters that

Table 5. **Factor level ranges investigated for the scoping study**[a]

potential QCPP	ranges	mild	centre	forcing
*casopitant impurity profile	numerical	(standard)	(mid-purity)	(customised)
*agitation rate as *P*/*V*	W/m^3	40	180	320
*ethyl acetate amount (vol)	1.5−3.5[b]	1.5	2.5	3.5
*acetone amount (vol)	3.5−5.5	5.5	4.5	3.5
isooctane amount (vol)	2−4	2	3	4
*seed quantity (wt)	0.25−0.75	0.25	0.5	0.75
seed attributes	batch and micronized seed	parent seed	parent and micronized	parent seed
*seeding temperature (°C)	30−50	50	40	30
*ageing time after seed addition (h)	0.5−2.5	2.5	1.5	0.5
isooctane addition time (h)	0.5−1.5	1.5	1.0	0.5

[a] Agitation rates were adjusted to take into account the changes in reactor occupancy. [b] Volumes in the table are referred to 0.86 wt of casopitant. * Refers to the parameters studied in Study a (section 6.3.1).

could ultimately affect the API critical quality attributes (CQAs) reported in section 3. These parameters are referred to as potential QCPPs.

The process resulting from the early crystallization development can be summarized by the following working directions. Casopitant free base in ethyl acetate and acetone is heated to 40 °C, methanesulfonic acid is added and the solution seeded. The slurry is aged for an hour followed by the addition of isooctane over the same time. The slurry is cooled to 25 °C and then filtered, washed, and dried under vacuum.

Amongst the process parameters that could affect the API CQAs, the following parameters were identified as potential QCPPs

(i) impurity profile of the input casopitant free base
(ii) agitator rate expressed as power per unit volume, *P*/*V*
(iii) ethyl acetate amount
(iv) acetone amount
(v) isooctane amount
(vi) seed quantity
(vii) seeding temperature
(viii) ageing time after seed addition
(ix) isooctane addition time

6. Sequential and Iterative Experimental Programme

The quantitative effect of the potential QCPPs on the CQAs was investigated, systematically building knowledge and confidence through a series of experimental studies. By adopting this philosophy, any group of experimental runs was only part of an iterative sequence of events, and the strategy was aimed at the overall furthering of knowledge at each juncture, rather than the success of any individual group of experiments. It was important to organise these studies such that we were, in due course, likely to be led to the right conclusions even though our initial choices of the region of interest, the metrics, transformation, and levels of the input variables may not have all been ideal. The path to success was not unique. It was not the uniqueness of the path that was of importance here; rather it was the probable and rapid convergence of an iterative sequence to the right conclusions in supporting the definition of design space. The following sections highlight the studies that were performed leading to the definition of design space and there from the control space/strategy.

6.1. Scoping Study. An initial scoping study was performed to test the crystallisation and analysis methods prior to committing time and materials to the eventual experimental design campaign as well as getting a feel for the appropriateness of the factor range settings (Table 5). The study also served a dual purpose in determining whether the mixing was important and the choice of the best experimental platform. According to some preliminary mixing modelling studies, a 2-L reactor configured to mimic full-scale plant kit was used to perform these crystallization experiments. This was achieved through maintaining geometric similarity and operating under conditions scaled in accordance to accepted chemical engineering principles, e.g. using the constant power-per-unit volume (*P*/*V*) principle for scaling agitation rate.

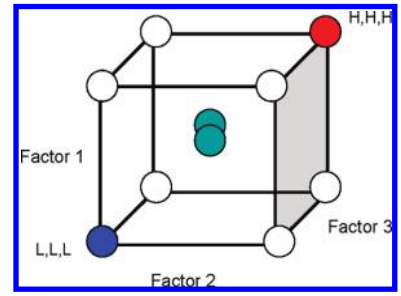


Figure 1. **Scoping study runs.**

The experiments that constituted a scoping study included two control reactions run close to the midpoints of each factor range providing an estimate of the background variability in the system with two extreme sets of reaction conditions representing the two forcing experiments (same experimental conditions except for the stirring regime) and two mild experiments (same experimental conditions except for the stirring regime) as demonstrated in Figure 1.

Further to this, to confirm the effect of seed particle size distribution (PSD) on the API attributes, two different seeds were used at the centre points (a representative API batch produced during process development: parent seed and a micronized batch). Seed response studies previously performed clearly indicated dependency of the API PSD with respect to the seed attributes and loading.

The rationale guiding the mild and forcing conditions was based on the level of supersaturation; at mild conditions the process parameters were set so as to keep the level of supersaturation low.

The process parameters and their ranges are reported in Table 5.

6.2. Findings from the Scoping Study. The analyses of the scoping studies and the following studies were based on

online (FBRM, imaging, IR, temperature, and stirring rate) and offline measurements (HPLC, NMR, GC, residue of ignition, XRPD, PSD, thermal analysis, surface area, microscopy, moisture sorption).

From the initial scoping study, it was clear that

(i) There was high variability in the responses of the extreme conditions experiments, and this suggested that the magnitude of the selected ranges should have been reduced to ensure lower variability and improve the process robustness.
(ii) The centre point replication indicated low variability in the resulting API properties.
(iii) Agitation affected the API PSD at mild conditions but not at forcing. This suggested a possible effect of agitation rate at one of the extremes of the evaluated experimental region.

The effect of seed attributes was confirmed by the comparison of the centre points: API PSD was affected by seed attributes. In particular, micronized seed reduces the API PSD significantly.

6.3. Modelling Studies Linking API CQAs and PSD with Process Parameters and Material Attributes. To simplify the crystallisation process, the next study was divided in two parts, (a) and (b). Parameters that were shown to have an effect on the API CQAs or other physical properties in (a) were then taken forward in the second study, (b), together with factors not considered in (a)—these were related to the addition of isooctane. Whilst this strategy may have posed complications in the evaluation of factor interactions, a calculated consideration of the crystallisation process deemed that the contribution to the resulting outcome induced by isooctane addition could have been considered separately from the rest of the process being solid crystallisation close to completion prior to the isooctane addition.

One single representative batch was used as seed in this and all subsequent studies as it was considered to be typical for this process.

6.3.1. Study (a). The effect of seven factors on the crystallisation was evaluated through a 20-experiment 2_{IV}^{7-3}fractional factorial design with four centre points. This was performed using two 2-L reactors that were geometrically similar to those of the manufacturing plant as reported earlier. The factors with associated ranges are highlighted by asterisks in Table 5, with API CQAs specification requirements summarized in Table 3. The isooctane addition rate and amount were held constant at the centre point conditions.

The main summary outputs from this study were the following:

(i) Impurities in the final drug substance were controlled primarily by the impurity profile of the starting material and to a lesser extent by the amount of ethyl acetate. As observed by comparing the HPLC profiles of the starting material and the resulting APIs, most of the impurities were poorly soluble in the crystallization solvents.
(ii) PSD outcome was controlled mainly through the amount of acetone, seeding temperature, and impurity profile of the starting material. This chiefly affects the degree of supersaturation at the seeding point when crystallization begins. Higher acetone amount, higher seeding temperature, and lower purity of the crude starting material reduce the degree of supersaturation favoring crystal growth.
(iii) All other responses and API CQAs in particular are within the limits of specifications.

6.3.2. Study (b). Following study (a), study (b) evaluated those factors (predominantly main effects) from (a) that were shown to affect impurity levels and PSD as well as both the isooctane amount and isooctane addition time (Table 5). As a result, a 10-experiment 2_{III}^{6-3} fractional factorial design with two centre points was conducted using the same equipment. Ambiguity from confounding of significant effects (isooctane addition time aliased with the interaction of acetone amount and seeding temperature, and isooctane amount with the interaction of impurity profile and seeding temperature) led to conducting another four experiments, paving the way towards achieving a higher level of confidence in the modelling of each CQA and those involving the PSD. For each experiment, the seed quantity, agitation rate, and ageing time after seed addition were held constant at the mid-range conditions as they were shown in study (a) to have little or no practical impact.

The analysis of the results from the augmented study (b) suggested that the factors that governed the effect of the API CQAs and particle size distribution (PSD) were solely the following:

(i) casopitant free base impurity profile
(ii) ethyl acetate amount
(iii) acetone amount
(iv) seeding temperature

The lack of evidence of global curvature resulted in a decision not to expend further resources in individually modelling those factors identified as being significant to the API CQAs and PSD. Ageing time after seed addition appeared to have a borderline effect on the span of the PSD not considered in this paper. After careful consideration through risk assessment, a conservative measure was taken in retaining it for the control strategy (see section 9 discussion). With regards to the impact of these potential QCPPs against the casopitant impurity profile, only impurity **3** was found to be affected by them, whereas others mentioned in Table 3 were unaffected.

7. Design Space Definition for the Crystallisation Process

In recent years, the concept of Design Space has received much attention in the pharmaceutical industry. In particular, within the ICH Q8 Guidance, "Design Space (DS)" has been defined as "the multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality." Here assurance implies a high probability of the Critical Quality Attributes (CQAs) all simultaneously meeting their specification requirements. It further states that: "Working within the DS is not considered as a regulatory change. Movement out of the DS is considered to be a change and would normally initiate a regulatory post approval change process.

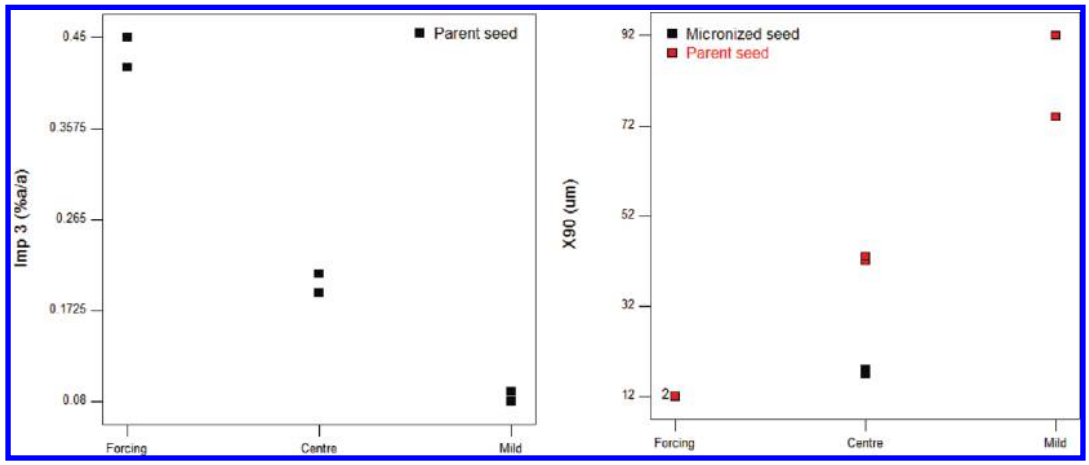


Figure 2. **Exemplification of responses resulting from the scoping study: Imp 3 amount and API PSD - X90.**

The rather vague ICH definition of DS has left the door open to numerous interpretations and implementations. For some, there appears to be a feeling that DS's can be constructed using the "Overlapping Mean Responses" (OMR)[6] approach. In this simplistic method, the overlapping response surfaces (e.g., by way of contour plots) are used to ascertain a "sweet region" where the mean response surfaces possess a region of overlap with a desirable multiple-response configuration. The OMR approach to create an example of a DS can be found in the ICH Q8 guidance document, Pharmaceutical Development, Annex to Q8 (2007). Figure 2c in Appendix 2 of the ICH Q8 Annex shows an overlay plot for a granulation operation with two quality responses, friability and dissolution. The figure title taken from the ICH Q8 Annex states: "Potential process design space comprised of the overlap region of design ranges for friability and or dissolution".

There is an abundance of examples of OMR plots in popular text books on experimental design and response surface methodology although such books predate the ICH Q8 DS issue and do not address themselves specifically to the DS problem. Another reason for their popular use is that OMR plots are easy to create using off-the-shelf software such as Design Expert and SAS/JMP in which slider tabs allow the user to change the values of the third, fourth, etc. predictive factors to see the cross-sectional changes in the OMR surface plot. See Peterson and Lief[6] for a thorough discussion.

The OMR approach has been illustrated for the casopitant mesylate crystallisation in the trellis plot of Figure 3 for the API CQAs and PSD in which seeding temperature and acetone ranges are depicted for combinations of ethyl acetate amount and input impurity profiles. The "yellow sweet region" (Figure 3) derived from those models in study b) (section 6.3.2) is often mistaken to be an area where high confidence can be assumed throughout. However, such regions harbour conditions on or close to the boundary that provide poor likelihood of meeting all specification requirements simultaneously. These reliabilities can be roughly on the order of 0.5^r where r is the number of response attributes.[6]

In addition to OMR plots, "Desirability Functions (DF)"[7] have been used in a similar context. These functions map the mean responses onto a scalar desirability function which is typically the geometric mean of individual desirability functions. Both approaches have been shown to have serious flaws. First, they do not account for the model parameter uncertainty, which can be substantial.[8] Second, they ignore the correlation structure of the regression model residuals, which can have serious consequences.[6] More specifically for DS's, neither the OMR nor the DF approaches provide a way to quantify the level of assurance of meeting product specifications. This does not seem justified given that the ICH Q8, Q9, and Q10 guidance documents[1] are inundated with the words "risk" and "risk-based". For any DS constructed, surely the core definition of design space begs the question, "How much assurance?" How do we know if we have a "good" design space if we do not have a methodology for quantifying "How much assurance?" in a scientifically coherent manner?

In this paper we adopt the Bayesian predictive approach to define DS[12] which overcomes the shortcomings of both the OMR and DF approaches by simultaneously incorporating correlation among the attributes at each fixed operating condition, model parameter uncertainty, and many sources of input and process variation and provides a measure of assurance for meeting process and/or material specification requirements.[9−12] A summary of the main features of this approach has been captured in an article by Peterson[10] in his Figures 1 and 2 entitled "Multivariate Distributions and the Role They Play in the Design Space Reliability".

(6) Peterson, J. J.; Lief, K. The ICH Q8 Definition of Design Space: A Comparison of the Overlapping Means and the Bayesian Predictive Approaches. *Stat. Biopharm. Res.* **2010**, *2*, 249–259.
(7) Derringer, G.; Suich, R. Simultaneous Optimization of Several Response Variables. *J. Qual. Technol.* **1980**, *12*, 214–219.
(8) Hunter, J. S. Discussion of Response Surface Methodology: Current Status and Future Directions. *J. Qual. Technol.* **1999**, *31*, 54–57.
(9) Stockdale, G. W.; Cheng, A. Finding Design Space and a Reliable Operating Region Using a Multivariate Bayesian Approach with Experimental Design. *J. Qual. Technol. Quant. Manage.* **2009**, *4*, 391–408.
(10) Peterson, J. J. What Your ICH Q8 Design Space Needs: A Multivariate Predictive Distribution. *PharmaManufacturing* **2009**, *8*, 23−28. (Available online at: http://www.pharmamanufacturing.com/articles/2010/097.html?page=full).
(11) Del Castillo, E. *Process Optimization: A Statistical Approach*; Springer: New York, NY, 2007.
(12) Peterson, J. J. A Bayesian Approach to the ICH Q8 Definition of Design Space. *J. Biopharm. Stat.* **2008**, *18*, 959–975.

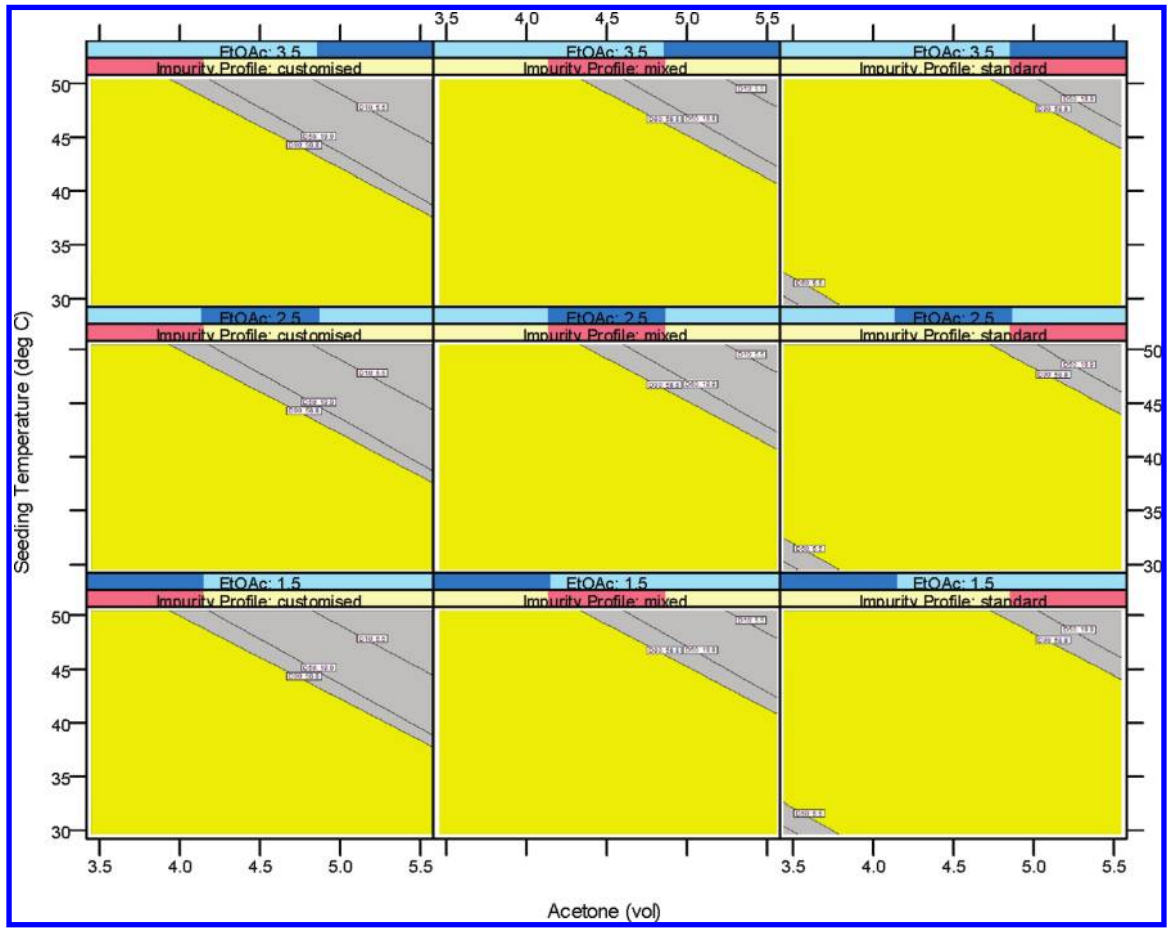


Figure 3. **Overlapping mean responses approach.**

The output from a Bayesian predictive approach derived from the same data and models as that used for the OMR approach is illustrated in Figure 4, in which the contour lines represent the levels of assurance (as a probability) in meeting API CQAs and PSD specifications simultaneously over the region of interest. It clearly highlights that the process is not robust over the original yellow "sweet region" as initially thought using the OMR approach of Figure 3. There appears a smaller sub-region where the process is more likely to produce material that meets the specifications at higher levels of assurance, for example an assurance greater than 0.8 (equivalent to 80%). For this level of assurance, the customised impurity profile would not be able to deliver material capable of meeting the specification requirements (Figure 4).

There are no hard and fast rules in defining the level of risk that would be tolerable in defining the boundaries of the crystallisation DS or for that matter any other manufacturing process. The ICH Q8 Guidance does not state precisely how much "assurance of quality" a DS should have. Peterson[12] does, however, provide a "thought experiment" regarding the possible levels of assurance associated with the traditional "three validation batches" approach in which he surmises that a reliability of 0.8 is (historically speaking) a sufficiently large reliability for manufacturing validation.

Note, the data used for the OMR and Bayesian predictive approaches are available as Supporting Information, with Design Expert (v. 7.1.1), R (v. 2.5.1), and SAS (v. 9.1) used for the data manipulation and modelling and S-PLUS (v. 7.0) for the graphical representations in Figures 3 and 4.

8. Implementation and Operation within Design Space

Although the trellis contour plot (Figure 4) provides an invaluable aid in visualising the crystallisation design space for a preselected reliability, the task becomes ever more difficult to visualise and to manoeuvre practically for an operator as the number of dimensions increases beyond three. A simplistic way to tackle this problem would be to define the design space as a series of fixed ranges created by arbitrarily inscribing a hyper-rectangle (generalization of a rectangle for three or more dimensions) such that any permutation of factor level settings was to achieve a sufficiently high level of assurance of meeting specification limits. For example, this could constitute the edges of the white rectangles shown in Figure 5 to ensure that all of the input material attribute eventualities (customised, standard, and mixed) were accounted for.

These fixed ranges could then be used as a baseline to inscribe further hyper-rectangles characterising "normal operating ranges" (NOR) of process parameters within which the parameters are routinely controlled during production. This would experimentally define the control strategy (CS) of the drug particle forming.

In this example, Figure 5 shows that there are conditions within the DS that only lead to an assurance of around 0.65

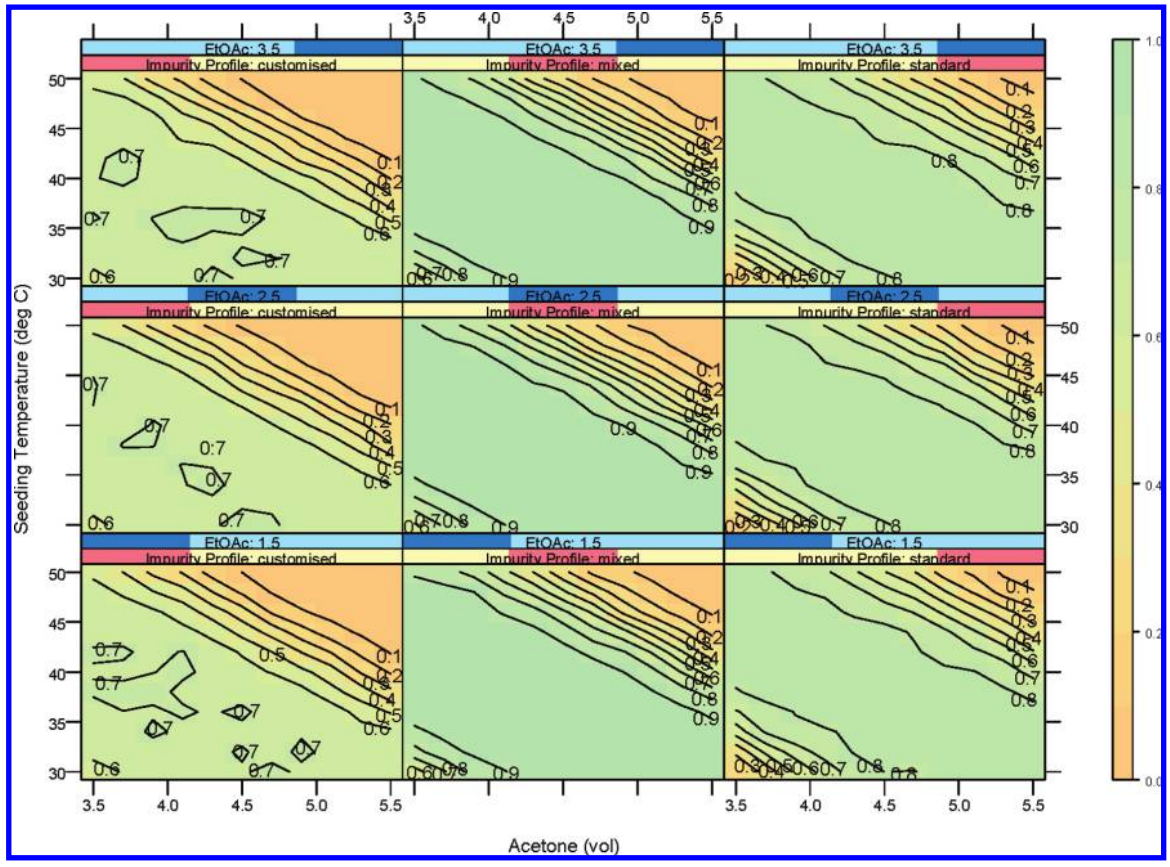


Figure 4. **Bayesian predictive approach.**

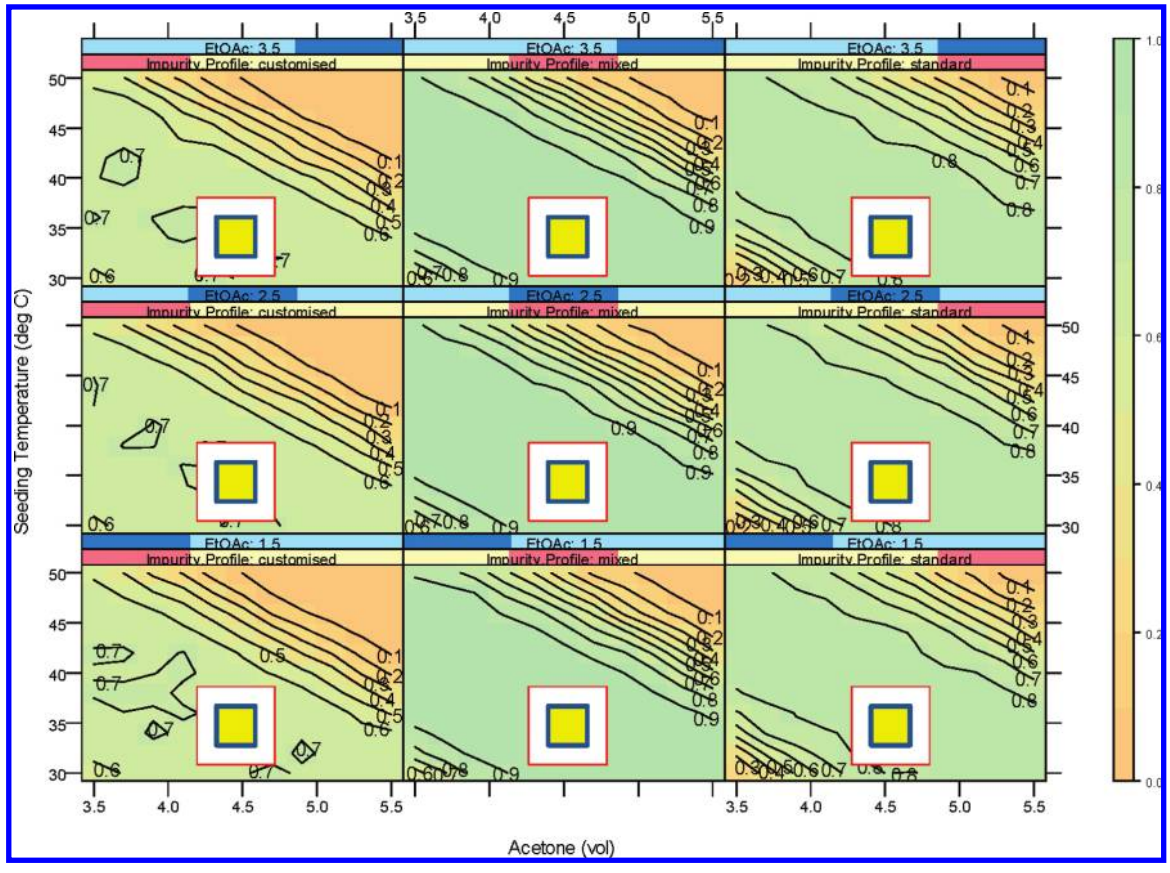


Figure 5. **Restricted design space region defined by fixed operating ranges.**

(65%) of meeting the specification requirements simultaneously. Although this could represent a significant risk to the patient, the low level of assurance is attributed to the PSD values and not the impurities which formed the CQAs. As the PSD is not

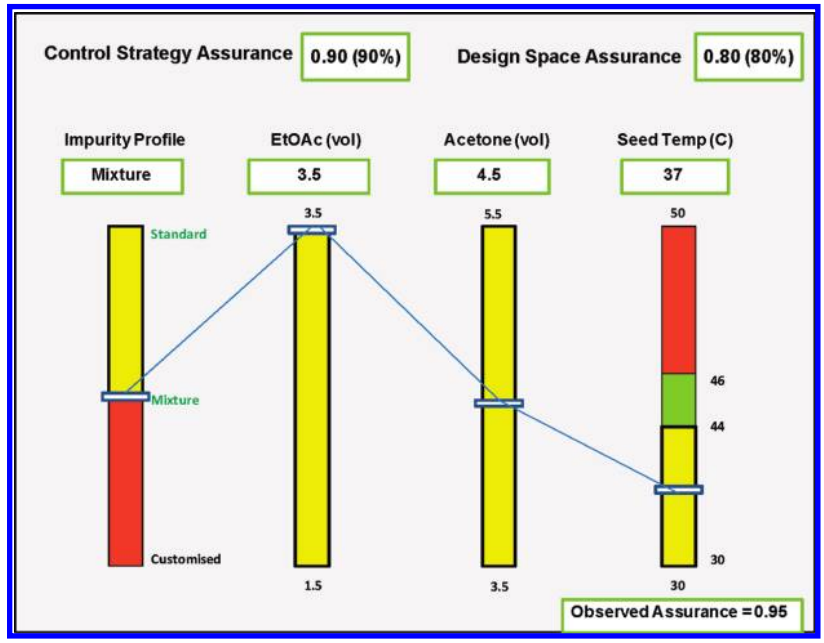


Figure 6. **Example 1: sequential crystallisation operation using flexible ranges.**

related to safety or efficacy, and simply processing characteristics, this level of risk might be considered to be acceptable.

This traditional type of definition of NOR and PAR's (Proven Acceptable Ranges) has found popularity within the pharmaceutical industry as it has allowed companies to graphically illustrate sectional representations of DS's as well as documenting ranges univariately in a table to regulators as part of a new drug submission. However, if the DS had a long "drawn out" diagonal form, then inscribing a hyper-rectangle would only comprise a disappointingly small part of the DS. Stockdale and Cheng[9] propose using a series of several inscribed rectangles to cover a larger part of the DS. Unfortunately, if the DS has multidimensions and an odd shape, construction of such a series of hyper-rectangles in an optimal manner could not only be problematic but would still unduly limit the scope of operation and manufacturing flexibility that the regulatory agencies are advocating. These constraints could ultimately restrict process improvement activities that may be beneficial to the manufacturer and the patient.

A more efficient and natural solution in defining DS and CS would be to consider these regions as taking no fixed shape but simply defined as boundaries of assurance. For example, DS could be defined as all those factor level combinations for which there was at least an 80% chance of meeting CQA and PSD specifications simultaneously. As the CS would normally constitute a region within the DS where routine operation would take place, a higher level of assurance could be defined for the CS, say 90%. The implementation of this model based approach (also referred to as parametric control[2]) would be relatively straightforward to implement. In the background it would consist of a flexible electronic spreadsheet[10] specifically constructed for the DS and CS at hand with a user-friendly interface (Figures 6, 7 and 8) that the plant operators would use to operate and control a process.

Generally, as batch unit operation processes are sequential, then any current operation of a process can be carried out based on the conditions used for the previous operation. This would enable complete flexibility of operation within the DS/CS of assurance. The approach would provide the operators with the required ranges for subsequent operations based on the input (previous values from the sequential process) provided. The approach could also be extended to take advantage of including manufacturing attributes such as time and cost. Stockdale and Cheng[9] have referred to this as a reliable operating region (ROR) where important manufacturing criteria are also satisfied in addition to quality attributes. In principal, the ROR will lie within the Design Space and the reliability/assurance would be quantified as the joint probability of meeting both API specifications and desirable manufacturing attributes.

An example of the output from this approach has been exemplified in Figure 6 where CS and DS assurance boundaries of 0.9 (90%) and 0.8 (80%) respectively, have been selected as the minimum joint probability of all the CQAs and PSD values meeting specifications. For this level of assurance, only the standard and mixed impurity batches can be selected as input into stage 2d as the customised batch would not deliver on the minimum levels of assurance required (Figure 6).

Supposing a mixed input profile batch of casopitant was selected, then, any amount of EtOAc between the range 1.5−3.5 vols could be charged without compromising the chosen boundary reliabilities. In general, the batch record would target an addition by the operator somewhere close to the midrange (∼2.5 vols of EtOAc). Suppose for some reason, the actual amount of EtOAc charged was 3.5 vols, then any range of antisolvent (acetone) between 3.5−5.5 vols would be acceptable. If the actual recorded volume of acetone was 4.5 vols, the next processing step would require the seeding temperature to remain within a range of 30−44 °C, to ensure a reliability of at least 0.90 being maintained. It is important to notice that although the controlled range for seeding temperature would be 30−44 °C (yellow range) under routine production, the design space range would be 30−46 °C (green range). This would suggest

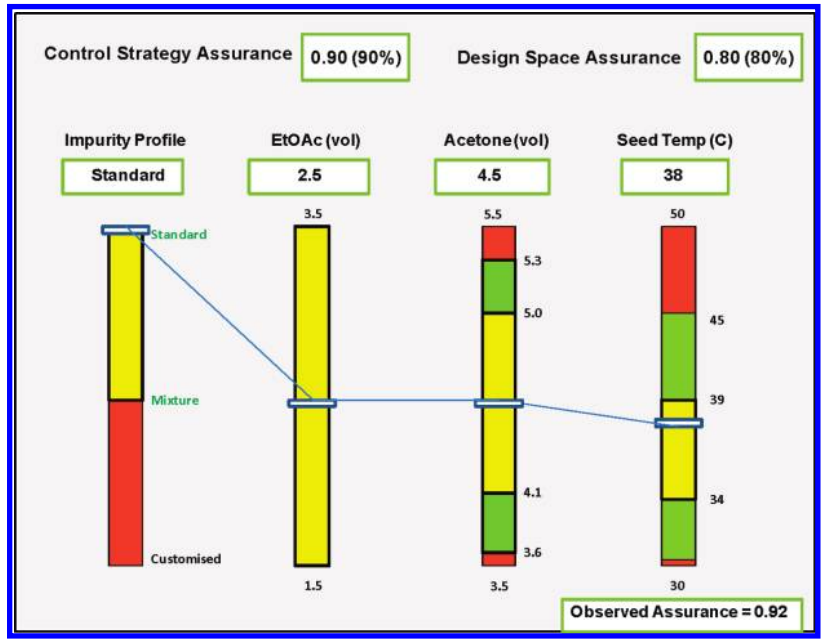


Figure 7. **Example 2: sequential crystallisation operation using flexible ranges.**

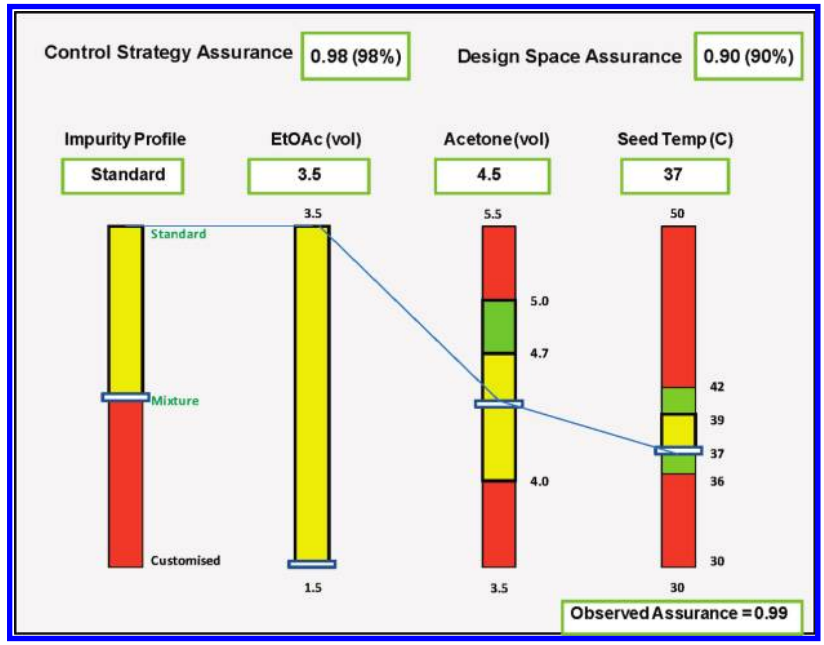


Figure 8. **Example 3 sequential crystallisation operation using flexible ranges.**

a seeding temperature between 44−46 °C would be accommodated without regulatory approval. Let us say for this operation a seeding temperature of 37 °C was selected, the actual factor settings lead to a probability of 0.95 (95% assurance) of all the CQA and PSD requirements being met.

To further demonstrate the batch record flexibility for the same levels of control strategy and design space assurances as in example 1 (Figure 5), Figure 6 shows the levels of acetone volumes and seed temperature ranges that could be tolerated by the robustness of the process. Again the yellow region embodies the control range that the operator would be expected to achieve, with a leeway representing the green design space ranges that would not require any further regulatory approval.

Figure 8 shows a third example in which a greater degree of confidence requires a tighter control on both the Acetone amount and seeding temperature.

Although we have simplified the concept of the CS as a region within the DS where routine operation takes place, the Control Strategy may well contain many other components to ensure the process delivers the required CQA values. The elements and relationships of DS and CS to the CQAs are shown schematically in Figure 9.[1]

9. Verification Experiments

From information derived on the levels of risk in the preceding sections, a number of confirmatory/verification experiments were performed at representative scale to confirm scalability. The positive outcome of these trials reinforced belief of the experimental work and laid the foundations for a subsequent implementation of a successful control strategy. A final risk assessment (ICH Q9) was conducted on the accumulated data in arriving at the decision that ethyl acetate

Figure 9. **Interdependencies of CQA's, control strategy and design space.**

amount, acetone amount, seeding temperature and ageing time after seed addition were quality process parameters (QPPs)[13] [definitions reported in the Glossary]. A set of ranges (Table 5) were defined for this part of the overall control strategy that GlaxoSmithKline proposed for assuring product quality in their QbD regulatory submission. In addition, ageing time was conservatively included as a QPP for its effect on the span of the PSD though had little impact on the actual CQAs and PSD measurements of D10, D50, and D90.

10. Control Strategy

The studies described in this paper have successfully led to the definition of the control strategy for stage 2d of the casopitant mesylate manufacturing process. In conclusion, Table 6 summarizes the control strategy for this stage against the drug substance CQAs.

11. Conclusion

Recent guidance for industry from the regulators such as the Critical Path Initiative, FDA's cGMP for the 21st Century, the Process Analytical Technology Initiative and Quality by Design principles outlined in ICH have provided some broad strategies for the pharmaceutical industry in focusing towards a structured approach to gaining process knowledge and developing robust and reliable manufacturing control strategies. These principles have been applied successfully in developing a control strategy for stage 2d of the casopitant mesylate **1** manufacturing process. This process understanding has enabled the development of a control strategy that includes the implementation of a flexible design space.

12. Experimental Section

(2*R*,4*S*)-4-(4-Acetyl-1-piperazinyl)-*N*-{(1*R*)-1-[3,5-bis(trifluoromethyl)phenyl]ethyl}-2-(4-fluoro-2-methylphenyl)-*N*-methyl-1-piperidinecarboxamide Methanesulfonate Salt (Casopitant Mesylate 1). A solution of casopitant **2** (0.86 wt) was diluted with EtOAc (overall solution of **2** in EtOAc was 4 L) and acetone (4.5 L) and was heated to the required temperature (from 39 °C). Thereafter, neat methanesulfonic acid (0.12 L, 1.64 mol) was charged, followed by a slurry of **2** (0.005 kg) in EtOAc (0.05 L) as seed. The obtained suspension was stirred for 1 h followed by the addition of 3 L of isooctane in the required time (1 h). The slurry was cooled to 20 °C in 2 h and aged 3 h. The suspension was filtered and the solid washed with EtOAc (3 × 4 L). The white solid was dried overnight under vacuum at 40 °C to give the desired casopitant mesylate **1** (0.94 kg).

^{1}H NMR (600 MHz, DMSO-d_6) δ 9.57 (br s, 1H), 7.99 (br s, 1H), 7.68 (br s, 2H), 7.23 (m, 1H), 6.95 (dd, 1H), 6.82 (m, 1H), 5.31 (q, 1H), 4.45 (m, 1H), 4.20 (dd, 1H), 3.99 (m, 1H), 3.56 (m, 1H), 3.47 (m, 3H), 3.37 (m, 1H), 3.15 (m, 1H), 2.96 (m, 1H), 2.87 (m, 1H), 2.80 (t, 1H), 2.74 (s, 3H), 2.36 (s, 3H), 2.30 (s, 3H), 2.13 (m, 1H), 2.08 (m, 1H), 2.10 (s, 3H), 1.87 (m, 1H), 1.73 (m, 1H), 1.46 (d, 3H). MS: *m*/*z* 617 $[MH]^+$, as free base.

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Glossary

Drug Product Critical Quality Attributes or Drug Substance Critical Quality Attributes. Measurable properties of drug product or API that are critical to ensuring patient safety and efficacy. The property must be within a predetermined range to ensure product quality. A property which is measured outside the range indicates a batch failure.

Critical Quality Attributes. Measurable properties in the unit operation or stage inputs, stage outputs, device, etc. that

Table 6. **Summary of the control strategy for stage 2d**

	elements of control		
drug substance CQAs	starting materials and intermediates specifications	quality process parameters	drug substance specification
casopitant stereoisomer **3**	(*R*)-piperidone mandelate salt **7** (*R*)-amine **5**	EtOAc amount	yes
		acetone amount seeding temperature ageing time before isooctane addition	
casopitant stereoisomers **10,11**−**13, 12**−**14**			
azine related impurities **15**, **16** and **17**	1-acetylpiperazine		yes
crystalline form	controlled by the process procedure		yes

(as determined by risk assessment) present a **high risk** to the process falling outside the design space or proven acceptable ranges.

Quality Attributes. Measurable properties in the unit operation or stage inputs, stage outputs, device, etc. that (as determined by risk assessment) present a low risk to the process falling outside the design space or proven acceptable ranges.

Quality Critical Process Parameter. The process parameter that influences a critical quality attribute and (as determined by risk assessment) presents a high risk to the process falling outside the design space or proven acceptable ranges.

Quality Process Parameter. Process parameter that influences a critical quality attribute but (following a risk assessment) presents a low risk of the process falling outside the design space or proven acceptable ranges.

Control Strategy. A (planned) set of controls, derived from (current) product and process understanding that assures process performance and product quality. The controls can include parameters and attributes related to drug substance and drug product materials and components, facility and equipment operating conditions, in-process controls, finished product specifications, and the associated methods and frequency of monitoring and control. (ICH Q10 definition - words in brackets are felt unnecessary.)

Proven Acceptable Range (PAR). The upper and/or lower limits for process parameter or attribute values between which the parameter or attribute is known to produce a process output (e.g., intermediate, API, or DP) that meets the CQAs. The PAR may or may not represent the point of failure. The PAR for a given process parameter or attribute may be dependent upon the PAR values for one or more other process parameters or attributes (e.g., multivariate).

Normal Operating Range (NOR). The upper and/or lower limits for process parameter values between which the process parameter is routinely controlled during production. The NOR lies within the Proven Acceptable Range. The NOR for a given process parameter may be dependent upon the NOR values for one or more other process parameters.

(13) QPPs and QCPPs belong to the class of Critical Process Parameters as for ICH Q8.

Supporting Information Available

Table with the data of the experiments that were used to generate the plot and curves. This material is available free of charge via the Internet at http://pubs.acs.org.

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