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REVIEW ARTICLE

Part 3: Enhanced Approaches to the Development of the Control Strategy and its Implementation in the Manufacturing Process Description

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Abstract

A series of case histories from IQ consortium member companies will be presented to exemplify how the application of the ICH Q11 vision for enhanced Quality by Design (QbD) development of the active pharmaceutical ingredient (API) can lead to differentiated outcomes for elements such as the API supply chain and control strategy, and how changes to such outcomes are managed over the lifecycle. A series of articles will address "flexibility" and look to provide recommendations for the further development of the ICH Q11 vision. The focus of this work will address flexibility associated with the "Enhanced Approaches to the Development of the Control Strategy and Its Implementation in the Manufacturing Process Description."

Keywords ICH · Control strategy · Manufacturing process description S2.2 · Quality by design (QbD) · Process · Methods · Models · CMC · Design of experiment (DoE) · Kinetics · Design space

Introduction

For any commercial drug substance, a key element of the control strategy is contained in the manufacturing process description, expressed in the regulatory file in module 3 Section S.2.2. How the control strategy is expressed in the manufacturing process description can have a key impact on the flexibility available to the manufacturer [ref paper1].

For example, under an enhanced approach, scientific understanding can justify wider or one sided parameter ranges. Equally, rather than being fixed, the boundaries of the operating space can also be defined based on interrelationships with other variables and potentially defined by models. Likewise, an alternative control strategy using in-process controls of impurities or reaction endpoints (including via PAT) can be utilized.

The purpose of presenting these case studies from IQ consortium member companies is to illustrate how an enhanced development approach can lead to different options for expression of the control strategy through the manufacturing process description and its lifecycle management. As part of a holistic control strategy, such options can provide greater flexibility during manufacture than a traditional manufacturing process described by narrow, fixed ranges, and the examples described in the paper reflect the diversity of control strategy options available to manufacturers.

Case Study 1: Multifactor Process Understanding to Control Impurities

Introduction

A science and risk-based approach such as QbD has served to deliver robust and productive processes, to ensure that CQAs are appropriately identified and that the process, by nature of its design, will assure that the CQAs will be consistently controlled. It is ultimately within the realm of the control strategy

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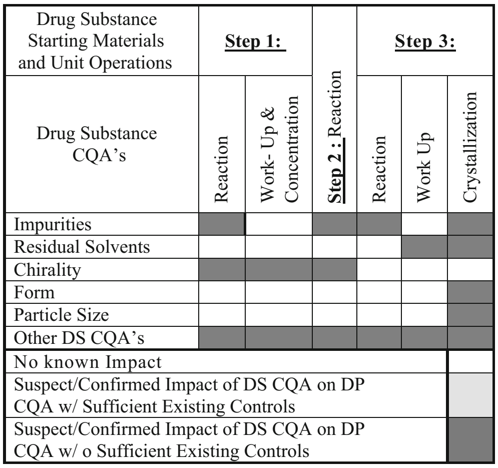
that several key questions can be addressed. These questions may fit within the general umbrella of assuring quality, but can often extend beyond this boundary.

QbD activities can be coupled with considerations for the commercial production facility in a way that can identify multiple potential control strategies of equal capability, but rely on the attributes of the manufacturing site to intersect with process understanding to arrive at the optimal choice for the control strategy at that specific site. Important considerations for the commercial production facility can include items such as (i) the management of rate limiting steps and vessel utilization towards optimized process cycle time; (ii) the balance of the cost of expensive reagents versus potential product yield gains; and (iii) evaluation of the process against equipment capabilities, including available methodologies for process automation and in-process testing.

This case study will focus on impurity profile as controlled by a GMP coupling reaction. In this study, we hope the reader will understand the iterative nature of the risk assessment process and the development activities that result from it. The associated development activities and results will be reviewed in order to highlight how information from various process steps and unit operations can be leveraged to work towards a comprehensive control strategy that considers the full spectrum of knowledge across all process steps. The case study will then show how multifactor process understanding, combined with the three major elements of control (raw material specifications, in process testing, and control that is intrinsically delivered by process design) can be combined into a control strategy that meets all criteria for quality, robustness, and productivity that is fully aligned with anticipated production sites.

Risk Assessment Activities

The risk management activities were aligned with the expectations of ICH Q11 [1], which calls for a cross correlation of drug substance CQAs from an understanding of the drug product CQAs and the corresponding formulation process. The potential drug substance CQAs are then interrogated against the contributing material attributes and unit operations (see diagram in Fig. 1). The level of knowledge informs whether there is a need to gather additional data to assure sufficiency of the control strategy; this aspect is beyond the scope of this case study. The row labeled "Impurities," in Fig. 1 shows which unit operations are likely to contribute to drug substance CQA impurities. The final reaction and crystallization in step 3 are the focus for the remainder of this discussion.



Drug Substance Starting Materials and Unit Operations	**Step 1:**		**Step 2 :** Reaction	**Step 3:**		
Drug Substance CQA's	Reaction	Work- Up & Concentration		Reaction	Work Up	Crystallization
Impurities	■	□	■	■	□	■
Residual Solvents	□	□	□	□	■	■
Chirality	■	■	■	□	□	□
Form	□	□	□	□	□	■
Particle Size	□	□	□	□	□	■
Other DS CQA's	■	■	■	■	■	■

No known Impact	□
Suspect/Confirmed Impact of DS CQA on DP CQA w/ Sufficient Existing Controls	▒
Suspect/Confirmed Impact of DS CQA on DP CQA w/ o Sufficient Existing Controls	■

Fig. 1 Identify DS CPPs from CQAs

Process Understanding and Control Strategy Development

The process flow diagram for step 3 is depicted in Fig. 2. There are a number of contextual details that should be kept in mind as the design unfolds.

Compound B in Fig. 2 is the most expensive reagent in the process, and on a mass basis, is approximately three times the cost of Compound A. The economic advantage in this case would clearly be to operate with a slight excess of Compound A. The most worrisome impurity resulting from this reaction sequence is known as "Impurity 3" due to a known limited capacity to purge it downstream in the extraction and crystallization operations. The formation of this impurity is favored when the reaction is formed with an excess of Compound B; and there do not appear to be any other factors that impact the levels of its formation. Other impurities present were below ICH limits, before the crystallization, which would represent another purification opportunity before isolation of the final active pharmaceutical ingredient API. The final aspect to keep in mind is that much of the development work on unit operations was done in parallel and integrated later into a holistic picture of step 3.

The initial focus of DoE was a one half factorial four factor DoE (Table 1). All parameters were defined on a scale-independent basis (e.g., concentrations vs. specific charges), and the DoE reserved additional factors to resolve interactions or curvature as opposed to starting with a full factorial approach. One factor at a time experiments were used at the center point to look for mixing sensitivity (not suspected in

Fig. 2 Detailed Process Flow for Step 3

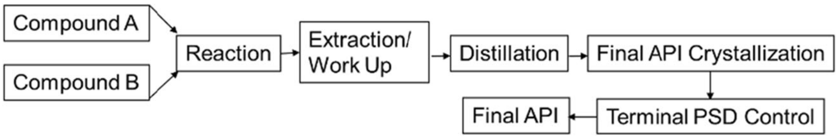


Table 1 Shows the range of experiments

Parameter	Units	DoE Range	Comments
A:B Ratio	Stoichiometric Ratio	0.93:1.0 to 1:1.0	Known to influence level of impurity 3
RXN Temp	Deg. Celsius	5 to 20	Known to impact overall impurity profile, but only suspected of impacting impurity 3
RXN Conc	L solvent per kg of B	18 to 22	Lower likelihood of impurity impact, may affect yield or cycle time
Water	L DIW per kg of B	4.5 to 6	

this reaction) and evaluate other parameters that were not believed to be implicated in any multifactor interactions.

The DoE runs gave generally satisfactory results. Twelve of the 14 runs did not show formation of any detectable impurity 3. Running the reaction at a 1:1, A:B stoichiometric ratio demonstrated formation of impurity 3, as did the experiment with higher amounts of A in conjunction with reaction temperature. There was a need to improve rigor around the fundamental understanding of impurity 3 formation, in order to confirm that there were no dispensing errors or other slight differences in A:B ration. A greater clarity was also needed around some of the model predictions in that the contour plots from the DoE (Fig. 3) show formation of impurity 3 where it is known not to be possible. To gain the necessary clarity, a repeat set of experiments was run at the previous DoE conditions, along with evaluation of intermediate temperatures and stoichiometric ratios to add curvature to the model. In addition, higher A:B ratios were studied in order to identify optimum yield conditions.

Experimentation continued until the variability in the key output responses, impurity 3 in this case were sufficiently explained in the model. Reaction performance at pilot and commercial scale at target conditions represented a multiple response optimum incorporating the formation of impurity 3, formation of total impurities, yield, volume productivity, and cycle time. From here, the effort shifted to analogous development data from the coupling reaction, extractive workup, and pure crystallization to understand the process design capability.

The concurrent development work on the extractive workup and the associated concentration were addressed using a one factor at a time format (no interactions in play). A seven-factor fractional factorial design was employed to characterize the final drug substance crystallization.

Key findings were that the organic phase could be heated and aged after the reaction prior to the extractive workup to ensure that all the product was in solution. It was also found that impurity 3 could be consumed, reducing by 0.5–0.6 LCAP over a 24-h period. Further, the crystallization design space was found to weakly reject the impurity (approximately 0.1–0.2 LCAP) at worst case parameter combinations.

Ultimately, there were several different ways of deploying an effective control strategy, given the knowledge of the step that was generated. Rather than a single set of commitments, flexibility was included to enable different sites to make equivalent material utilizing slightly different approaches:

The first aspect to consider was to whether to use passive control (leveraging the limited but measurable rejection capability of the impurities in the pure step) or active control, by adding a post-reaction range and an in-process control test that would enable routine operation in every part of the stochiometric and temperature ranges. The second alternative was to leverage the knowledge of the design space to constrain temperature but allow an expanded stoichiometric ratio (see Fig. 4).

The remaining option was to accept only the pure rejection activity and accept a narrow stoichiometric ratio, which works well for a more heavily automated facility with extensive site

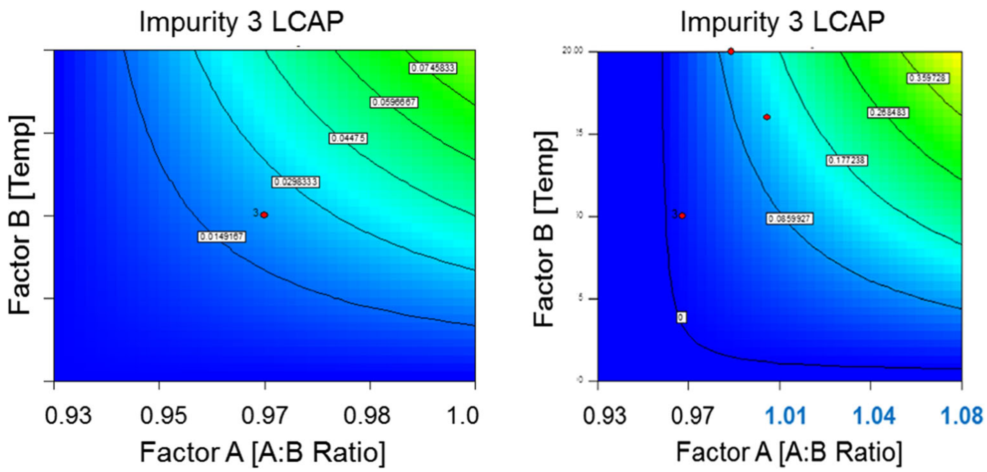


Fig. 3 Screening DoE model output (left) and post enhancement outputs (right)

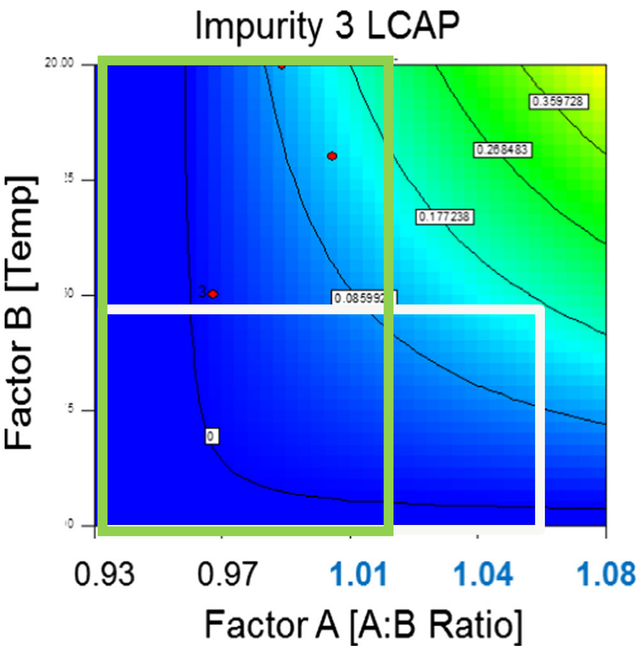


Fig. 4 Graphic representation of control strategy options

controls and automation capabilities. Less capable sites were able to leverage the same pool of process knowledge and implement the extended age with in process test. Both are equivalent with respect to controlling impurity load. Understanding each site and tuning the control strategy allowed a cost-effective control process that consistently delivers quality and can be tailored to the best use of flexibility for each individual manufacturing site.

Commercial lot manufacture at the respective sites enabled design space verification and leveraged the local PQSs as appropriate to change parameter targets within the design space limits.

Case Study 2: Manufacturing Process Description Flexibility

Introduction

The process description (commitments) section of the common technical document (CTD) (Section S.2.2 for drug substance, P.3.3 for drug product), bears particular importance as part of the overall Module 3 of an NDA submission [1]. The significance lies in the importance of commitments to the internal manufacturing controls and requisite ongoing documentation as well as external notifications that are required when and if an excursion outside of or a change to a designated parametric range occurs.

For this reason, to achieve appropriate flexibility, while assuring commitment to maintaining product quality, in the long term production of a synthesized chemical entity is paramount. The proper designation of parametric risk and the way in which the acceptable ranges are reported must carefully be documented in the proposed regulatory process description. Additionally, achieving a consistent approach to the methodology by which a process description is developed within an organization can lead to significant synergies when sharing information with regulatory bodies. In this case study, we will share an overview of our approach to maximizing potential flexibility without sacrificing accuracy of representing the significant components of a process control strategy to ensure acceptable product quality consistently over the lifecycle of an asset. In general, the process by which we execute the optimization phase of an asset lifecycle and reflect that in the registered process description consists of the following steps:

1) Develop detailed, iterative risk assessments to properly define risk level assigned to each process parameter.

    - Initial risk assessment to parse out parameters with no probability of impacting product quality versus all other parameters which may have a reasonable probability of impacting product quality.
    - Intermediate risk assessment to gauge relative risk of all parameters with the potential of impacting product quality. Quantify and categorize risk into three levels; low, medium, and high risk to impacting product quality.
    - Final risk assessment to gauge potential interactions of parameters categorized with a medium or high-risk categorization.
    - Assign a “Critical” designation to all parameters which maintain a “medium” or “high” risk designation after the entirety of the risk assessment process.

2) Determine appropriately sized proven acceptable ranges for sufficient process flexibility given manufacturing constraints and potential for longer term optimization and efficiency gains.
3) Determine the subset of in-process controls that are deemed “Critical” and designate CIPCs (critical in-process controls) versus IPCs (in process controls).
4) Construct the Process description based upon the assembled data set.

    - Non-critical parameters described in general terms of the governing unit operation rather than including numerical ranges.
    - Critical parameter’s ranges are captured in brackets [] and are in boldface in the text for emphasis.
    - Critical in-process controls (CIPCs) success criteria are in boldface in the text of the process description.

a) Risk Analysis

A significant body of information is available on methods of risk analysis [1] ref. Q9, Q11], and many case study examples of the various methodologies have been published [add references]. Specifically, the process by which we determined parametric risk involves initially establishing the critical quality attributes (CQAs), and completing any planned optimization of the production process. Once this baseline has been established, the generalized approach to parametric categorization is shown schematically in Fig. 5.

Initial Parameter Categorization For the initial parameter categorization, prior knowledge, experience with the current process, and experience with related processes allow for an initial characterization of the risk level for process parameters. Process parameters are characterized in this initial risk assessment as those of no risk and those of potential risk. This effort is done conservatively to ensure inclusion of all parameters that may pose risk to meeting the critical quality attributes of the drug substance.

Univariate Parametric Risk Assessmen After performing the initial risk assessment, proven acceptable ranges (PARs) are determined for any parameter designated as a "potential risk" parameter. The majority of the PARs were mapped to ranges considered statistically improbable under common cause operational variability [2], or beyond, but not necessarily studied to the limits of failure for the process. Typical operational variability is defined as the level of variation from a set point that is expected from an equipment set. Studies were performed to analyze the equipment used for various processes, at various scales, and for a variety of unit operations to determine the expected variability. Initial estimates of variability were based upon both internal and external benchmarking efforts aimed at determining worst-case control scenarios for typical operating parameters. The values for variability are established as a baseline performance expected of manufacturing processing equipment. The strategy by which the manufacturing data was analyzed to determine variability is the subject of several publications [2, 3]. Assuming all other parameters are held at their target set points, the probability of a parameter falling outside a weighted operational variability range (denoted by $\pm k\,\sigma$), when subject to common cause variability, is very small for large values of k. After an examination of a variety of statistical distributions, $k = 6$ was chosen as a conservative weighting factor. The value of $k = 6$ ensures that at least 99.5% of the values of a given process parameter fall within the range used to evaluate the criticality of that parameter, even given severely skewed, nonnormal distributions of parameter values. If, through mining of historical data, it was determined that the range for a parameter was already studied to an appropriate extent and resulted in intermediate or drug substance meeting specification, then the result is documented and used to establish the PAR. For situations in which historical data was unavailable, mathematical modeling and/or experimental univariate or multivariate analyses were performed to establish PARs. For PARs determined through modeling or bracketing analysis (i.e., multivariate analyses where process parameters with theoretical additive impacts are perturbed simultaneously), the responses are multivariate in nature, and therefore conservative in their estimation of the univariate impact to an individual CQA.

Intermediate Risk Assignment After performing the univariate risk assessment and determining PARs for any parameter designated as a "potential risk" parameter, a more comprehensive determination of the parametric risk associated with an individual parameter is done through scientific judgment, analysis of the PARs relative to the predetermined operating capability, or analysis of responses from the failure mode and effects analysis (FMEA). The magnitude of the impact to relevant quality attribute of isolated and non-isolated intermediates to the drug substance CQAs are used to categorize the parameter as either high, medium, low, or no risk (Table 2).

Nearly all process parameters have the potential to impact CQAs to some extent when examined at extreme ranges. The process by which a parameter is deemed "critical" is based on a fixed set of criteria, taking into account both the breadth of a PAR and the relative impact to a critical quality attribute. Internally, parameters may be designated as no, low, medium, or high risk based on this analysis, but for the purposes of determining if a parameter is critical, all parameters that are designated as medium or high risk based on this assessment are considered critical process parameters (CPPs). To differentiate among no, low, medium, and high risk parameters, an analysis of the univariate responses across the PAR is compared to a fixed quality criterion to determine the parametric risk category. A comparison of the baseline response (process at target operating conditions) to the impact on a quality criterion when operating at a minimum distance of 6 σ from process target serves as the basis for categorizing parameters (Fig. 6).

A high risk parameter (red line in Fig. 6) is a parameter whose perturbation to six times the operating variability

Fig. 5 Generalized approach to parametric categorization

Table 2 Parameter risk levels

Risk level	Description	Criticality level
High	A parameter with a narrow proven acceptable range (PAR) where operation outside the PAR may occur under common cause variability. Operation outside the PAR has a high probability of producing drug substance that fails to meet CQAs.	Critical
Medium	A parameter with a sufficiently large PAR where operation outside the PAR is statistically improbable based on common cause variability. Operation outside the PAR has a moderate probability of producing drug substance that fails to meet CQAs.	
Low	A parameter with a sufficiently large PAR where operation outside the PAR is statistically improbable based on common cause variability. Operation outside the PAR has a low probability of producing drug substance that fails to meet CQAs.	Non-critical
No	A parameter with a sufficiently large PAR where operation outside the PAR is statistically improbable based on common cause variability. Operating at the limits of the PAR has negligible impact to relevant quality attributes compared to baseline conditions.	

would fail to meet the quality criterion. A medium risk parameter (yellow line in Fig. 6) is a parameter for which the response across the PAR showed an impact to the quality criterion of less than the specification limit and greater than half the difference between the specification limit and the baseline process response. A low risk parameter (green line in Fig. 6 is a parameter for which the response across the PAR studied showed minimal impact to the quality criterion of less than half the difference between the specification limit for the quality criterion and the baseline process response. A no risk parameter (blue line in Fig. 6) is a parameter for which the response across the PAR studied showed no impact to the quality criterion (flat response) between the specification limit for the quality criterion and the baseline process response. The analysis of the trajectory responses of the process parameters allowed identification of parameters with negligible impact to the quality attribute across the entire studied range relative to expected baseline performance. A negligible impact was assessed as the more conservative of a quality attribute response less than one standard deviation from baseline response, or a difference from baseline of not more than the expected analytical variability in the measurement of the quality attribute. The conservative inclusion of parameters for further study from the initial risk assessment resulted in parameters falling into this category during the intermediate risk assessment. Based on this analysis, parameters meeting this criterion were categorized as no risk to impacting the relevant quality attributes and are therefore omitted from any further analysis in multivariate studies and excluded from specific delineation in the committed process description. All parameters categorized as medium and high were designated as critical process parameters; low risk parameters were considered non-critical. Identified parameters having no risk are also considered non-critical and were not necessarily studied further as part of the multivariate analysis, but they were included in terminal bracketing studies.

Final Risk Assignment Following any multivariate studies of critical parameters, analysis of the data confirms the appropriate parameter risk assignments. In the event that the bracketing analysis reveals previously unidentified interactions, the

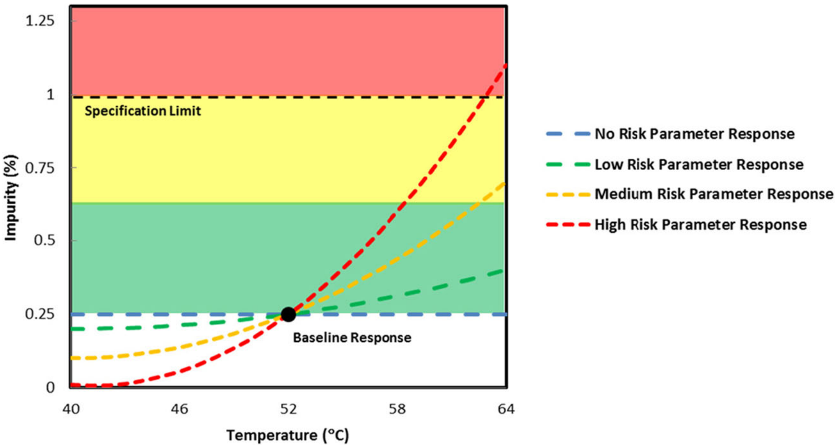


Fig. 6 Example graphical representation of the regions comprising response leading to a low, medium, high, or no risk designation for a process parameter

process is iterated with further PAR work, multivariate studies, and risk analyses.

b) Critical and Non-critical in-Process Controls

A critical in-process control (CIPC) is a test or measurement performed during production to monitor and, if appropriate, to adjust the process parameters or inputs to ensure drug substance critical quality attributes are met. Non-critical in-process controls are useful for assurance of cycle time and yield as well as process consistency but are not necessarily quality indicating.

The intended limits for CIPCs are determined through process robustness studies and impurity spiking or fate and purge studies. Impurity spiking and fate and purge studies are routinely performed with the intended manufacturing process to test the robustness of the designed impurity control strategy through the series of unit operations and purge points. Spiking studies are performed by introducing impurities known to be present in the starting materials or precursor intermediates for a particular transformation into various points in the synthesis. Additionally, potential impurities from known alternative starting material syntheses are spiked into the synthesis to test for purge capability for any potential starting material changes. Impurities were spiked at levels minimally equal to twice the levels established as acceptable in the starting material or precursor intermediates. Impurities that form as byproducts of the intended transformation are generated at elevated levels through perturbation studies as part of the PAR studies and multivariate analyses.

c) Flexible Process Description

An example of a flexible process description is included below. As noted, non-critical process parameters are described generally in terms of the unit operation. Critical process parameters are denoted in boldface with their appropriate proven acceptable range. Where appropriate, the acceptance criteria for the CIPCs is noted in boldface in the process description as well.:

Example: "Triethylamine is charged to form Compound B, and neutralize excess HCl to form triethylamine hydrochloride while maintaining the slurry temperature. The reaction mixture is cooled, and the triethylamine hydrochloride is removed by filtration and may be washed with cold tetrahydrofuran (THF). The filtrate and cake wash are combined and forward processed if **NMT 23.8%** area of Compound A remains. A catalytic amount of diisopropylethylamine (DIPEA) is added to the Compound B solution, and the solution is heated. A **solution of Compound C [1.06 to 1.25 mol Compound C per mol Compound B] in THF** is added to the Compound B solution and allowed to age until the reaction has **NMT 1.0%** area Compound C remaining."

Case Study 3: Flexible Scalability of a Hybrid Flow-Batch Process

In industrial processes, scale-up or down is considered successful when the process can achieve consistent performance across multiple manufacturing scales. The scalability of pharmaceutical unit operations is of major interest due to the limited predictability of demand and the need for scale flexibility, which have quality, regulatory, and cost implications. Scale-up or down issues may require costly post-approval changes, process revalidation, and additional stability data among others.

For commercial pharmaceutical processes, having the flexibility of moving across scales is vital not only to meet varying market needs but also to efficiently use multiproduct plants. In order to scale up or down a unit operation, a deep understanding of the scale-dependent process parameters that could negatively impact critical quality attributes is needed (i.e., identity, purity, particle size, form, etc.). Developing processes that are fully insensitive to processing conditions is not always possible, and a variety of methodologies and protocols to scale-up batch unit operations are explored industrially. Typically, dimensionless numbers, mechanistic models, experimentation, or combinations thereof are used [4–9]. Table 3 shows some of the most common considerations when scaling up chemical reactions.

For drug substance batch processes, limitations in heat and mass transfer rates (e.g., dispensing, warming-up), differences

Table 3 Typical considerations when scaling up chemical reactions

Reaction type	Scale-up considerations
Scale-up considerations	Residence time, contact time, or reaction time
	Mixing time (impeller power number *Po*, Reynold number *Re*)
	Material transfer time
	Overall heat transfer coefficient (*U*), heat transfer area (*a*)
Solid-liquid reaction	Residence time, contact time, or reaction time
	Material transfer time
	Agitation for solid suspension (critical stirrer speed for complete off-bottom suspension)
	Sherwood number (*Sh*) (mass transfer coefficient)
Gas-liquid reaction	Gas flow number (*Fl*)
	Mass transfer coefficient (*KL*) and mass transfer area (*a*)
	Impeller power number (*P*o)
Liquid-liquid reaction	Power per unit volume (*P*/*V*)
	Droplet size (*d*32)
	Sherwood number (*Sh*) (mass transfer coefficient) and mass
	transfer area (*a*)

in process cycle times, presence of multiple phases, mixing, and equipment configurations are listed as the main obstacles for successfully scaling-up [5]. With the introduction of continuous elements to pharmaceutical drug substance manufacturing processes, the focus of discussions regarding scale sensitivity has changed [10–13]. In flow processes, the pieces of equipment can sometimes be used from laboratory through pilot to production scale by simply increasing the overall production time or adjusting process parameters. Batch size is defined as a specific quantity of drug or materials that have uniform character and quality, within specified limits, and is produced according to a single manufacturing order during the same cycle of manufacture [14]. More often than not, the maximum batch size of flow processes is defined by available stability data and operational considerations (e.g., fouling) rather than equipment size.

In this case study, we describe the approach and recent experience at Eli Lilly & Co. to gain manufacturing flexibility when scaling-up a hybrid flow-batch drug substance process. The commercial process contained both flow and batch elements. For the batch elements, the process development history described in detail the manufacturing controls implemented and the methodologies used to: (i) ensure proper mixing of solid and liquid suspensions; (ii) achieve comparable mass and energy transfer rates across scales, (iii) justify how differences in cycle times are aligned with available stability data; and (iv) the use of seed material to promote growth-dominated crystallizations; etc. The aforementioned hybrid process contained three flow unit operations: a series of packed bed columns for metal sequestration, a tubular reactor for the thermal deprotection of the penultimate, and a final milling operation to control particle size of the final active ingredient. The following scale-up approaches were used for each unit operation:

Thermal Deprotection Reaction Performed in a Tubular Reactor

A mathematical model was used to define the design space [15]. The model was verified using independent laboratory and commercial scale data. Given the confirmation of the model assumptions that included activities during equipment qualification stage, the thermal deprotection was considered scale insensitive and the regulatory flexibility to scale-up or down was gained. The following model assumptions were considered:

- The thermally-induced deprotection of penultimate results in equimolar amounts of active ingredient, carbon dioxide, and tert-butanol. One of the considerations for model validity was to understand if some unexpected degradation reactions could occur at extreme reaction conditions (high temperatures and long residence times). In order to mitigate that risk, experiments were performed at worst case condition of the design space which produced acceptable quality material.
- The reaction takes place in a single liquid phase: pressure and temperature were controlled such that solvents are below the boiling point and CO_2 remains in solution. The relationship between pressure and temperature was studied both theoretically and experimentally to ensure this assumption was met.
- The reaction stream is well-mixed in the radial direction, but mixing in axial direction is negligible: The actual dispersion number ($D_n = D_{ax}/(vL)$, where D_{ax} is the axial dispersion, v is the fluid velocity, and L is the reactor length) was determined during equipment qualification by using tracer experiments. Simulations were used to determine the maximum dispersion number allowed that does not impact product quality, as shown in Fig. 7.

Metal Removal in a Series of Packed Bed Columns

While continuous packed bed column processes for removing dissolved species by adsorption are inherently transient operations, scale-up or scale-down of this type of adsorption processes is highly predictable when system thermodynamics and mass transfer resistances are well understood [16]. A mechanistic model for the metal sequestration step was developed and verified with laboratory and manufacturing scale data [15, 17]. Successful scale-up requires similarity of the processes thermodynamics and kinetics. While the thermodynamic properties are scale-

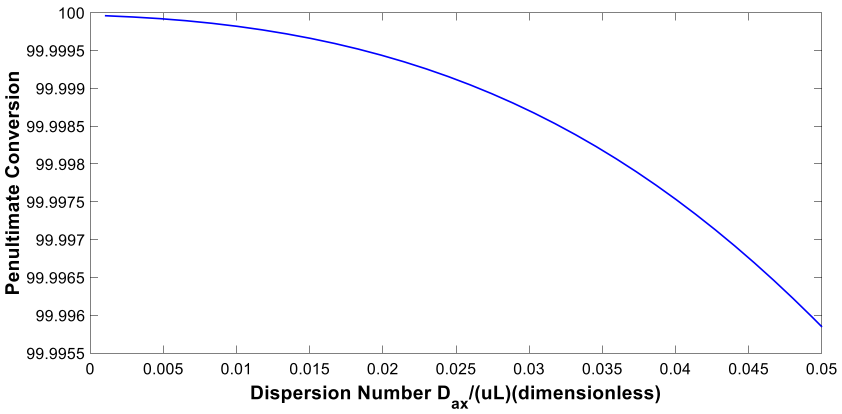


Fig. 7 Effect of dispersion number D_n on the penultimate conversion in tubular reactor

independent, kinetics are affected by scavenger particle size, packed bed column void fraction, superficial fluid velocity (also related to residence time), and overall system fluid dynamics. Manufacturing controls including characterization techniques and monitoring were in place to ensure particle size, residence time, packing efficiency, and resin efficiency were maintained when changing scales. Column axial dispersion and proper resin packing were determined at scale using tracer experiments, during equipment qualification. Change in scale requires using the model to predict the necessary length of column to ensure appropriate removal of soluble metal necessary to meet specifications in the drug substance for a given campaign size.

Milling

As a final step of the process, a continuous milling step is used to control particle size of the drug substance. Due to the inherently significant scale-dependence of milling unit operations and the lack of information about the effect of mill geometry and system fluid dynamics on particle breakage rate and breakage mechanism, only experimental data at manufacturing scale was used to determine process parameter's proven acceptable ranges and multivariate design space. In this case, changes in the mill equipment for scale-up or scale-down purposes will require process parameter risk reassessment and notification to regulatory bodies. From a unit operation perspective, the approach mentioned above was considered acceptable and provided the manufacturing flexibility needed.

Case Study 4: Design Space for Control of CQA Impurities in Drug Substance X

This example is intended to illustrate how the development of a design space for the acid hydrolysis of a late intermediate in the synthesis of drug substance X delivered flexibility in the context of a wider operating space. The example also illustrates how the approach could lead to a variety of potential control strategies. The example also illustrates how the development approach resulted in a control strategy which could be applicable to any site or scale, assuming some simple controls are in place for temperature and mixing of the homogeneous reaction.

Manufacturing Process to Drug Substance X The manufacturing process to drug substance X culminates in the telescoped process steps shown in Fig. 8. The intermediate 2 is saponified using aqueous sodium hydroxide before the resulting acetonide 3 is then hydrolyzed in turn by the addition of 6-M HCl. Drug substance X is then isolated following a work-up and salt formation.

A byproduct of the reaction is the ethyl impurity 5, formed via acid catalyzed reaction of drug substance X with the ethanol solvent. Both the intermediate acetonide 3 and the by-product, ethyl impurity 5, are impurity CQAs of drug substance X 4, as they failed to fully purge in the subsequent work-up and isolation.

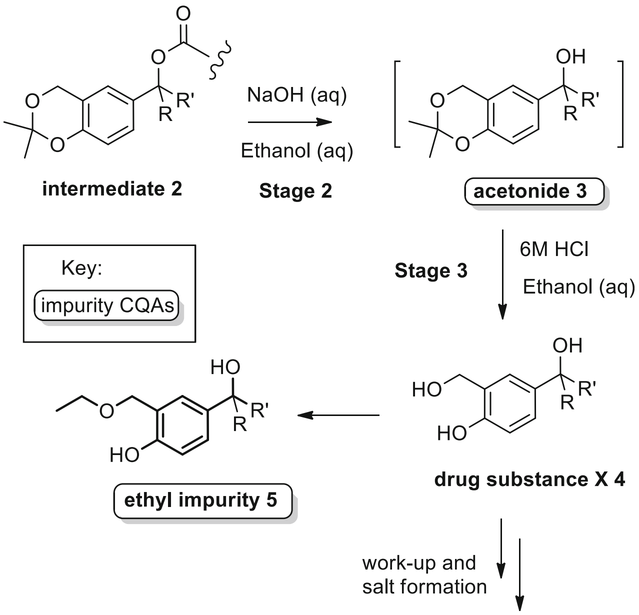
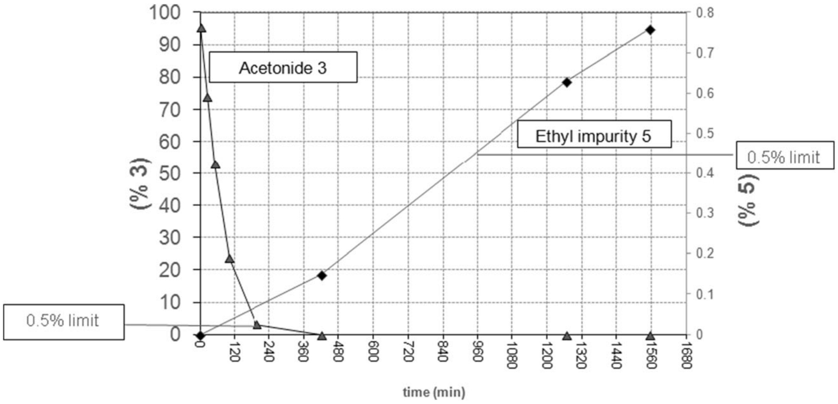


Fig. 8 Latter steps in the synthetic route to drug substance X, with CQAs indicated

Kinetic profiling of the reaction, as exemplified in Fig. 9 shows how levels of ethyl impurity 5 increase with time; whereas, longer reaction times will reduce levels of the stage 3 acetonide 3 input material, whose levels reduce following a pseudo first-order reaction rate. As such, an optimal time window exists for the reaction within which the acetonide 3 and ethyl impurity 5 levels are both sufficiently low to achieve the required quality in drug substance X. It was subsequently established through simple spiking experiments that, in order to achieve the acceptable limit for each impurity in the API, levels in stage 3 must be controlled for each to below 0.5%. Time is therefore a critical process parameter (CPP) for this reaction (Fig. 9), and the process must therefore be quenched within this "quench window" to achieve acceptable API quality.

It was subsequently established through a series of DoE and univariate experiments that the other PARs impacting levels of the two CQAs ethyl impurity 5 and acetonide 3 were the reaction pH and temperature. The control strategy for step 3 therefore requires control of the three CPPs of time, temperature, and pH. Within the aqueous ethanolic reaction environment, it proved challenging to deliver consistent and accurate measurements of pH at pH < 1 required for the reaction to occur. For this reason, a surrogate for the CPP of pH was controlled instead. Hence, reaction pH was controlled by initial titration of the NaOH/ethanol solution from stage 2 to approximately pH 2 (which could be accurately and consistently measured with any pH probe), followed by the addition of a set amount of 6.0-M HCl.

Fig. 9 Impact of time: kinetic profile for CQAs



Development of the Process Model Empirical process models for control of the acetonide 3 and the ethyl impurity 5 were then developed through a DoE approach. The DoE varied the 6.0-M HCl amount and the temperature. The lower and upper limits for the reaction time were established as an output of the experiments, through careful monitoring of the rate of consumption of acetonide 3 and of formation of ethyl impurity 5.

The design was a 2-parameter central composite design in 16 experiments with 4 center points and replicates of 4 other design points. Each of the experimental conditions used in the DoE are represented in Fig. 10:

The results from the experiments were used to develop two empirical process models for the reaction time, in hours, taken to reduce the level of acetonide 3 to 0.5% and to form 0.5% of ethyl impurity 5. These equations developed from the design are shown below:

$$\text{Acetonide 3 min } time = \left(\frac{1}{7.9 \times 10^{-4}A^2 - 0.013B^2 + 5.8 \times 10^{-3}AB - 6.9 \times 10^{-3}A + 0.08B + 0.05}\right)^2$$

$$\text{Ethyl impurity 5 max } time = \left(\frac{1}{2.0 \times 10^{-3}A^2 - 0.01B^2 + 0.02AB - 0.03A + 0.13B + 0.2}\right)^2$$

where: A = Reaction Temperature, °C; B = 6M HCl amount, vols (density of 1.1g/mL used);
Predicted reaction times are given in hours.

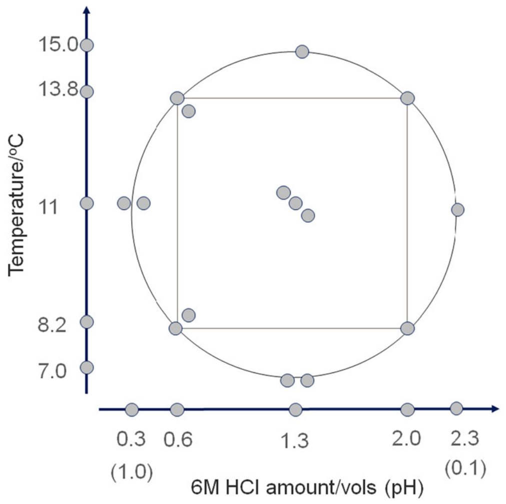


Fig. 10 Experiments run in the DoE

The first model describes the minimum reaction time (required to ensure that the acetonide 3 is controlled to below 0.5%) as a function of the amount of 6-M HCl, the temperature, and the time. A second model described the maximum reaction time (before the ethyl impurity 5 exceeds 0.5%) as a function of the same parameters. Both models assumed that the temperature was controlled isothermally throughout the reaction. In the production environment, such conditions were straightforward to control. The concentration of the 6.0-M HCl was controlled via a tight specification.

Figure 11 illustrates the models developed from these experiments as surfaces and shows how the time, temperature, and pH impacted on the minimum and maximum reaction times. The “quench window,” within which the reaction must be controlled, is represented by the volume between the two surfaces. Such a space can be described as the design space for control of the process and the two CQAs, as per the ICH definition of a design space.

An alternative illustration of the impact on allowable time reaction conditions is presented in Table 4. The table illustrates the restrictions of defining the process design space based on fixed ranges for the three CPPs: for example, at pH 0.3, across the narrow temperature range of 9–15 °C, maximum allowable time varies for 5 to 14 h. However, at pH 0.6 minimum times allowable varies from 4 to 13 h.

Each cell shows the upper 95% prediction interval for the minimum reaction time to achieve the maximum limit for acetonide 3, together with the lower 95% prediction interval for the maximum reaction time beyond which the maximum limit for ethyl impurity 5 would be exceeded. Upper and lower 95% prediction intervals reflect the worst case scenarios.

Figure 12 illustrates a smaller cuboid design space, defined by fixed parameter ranges within the broader “quench window” defined by the two process models. Registration of the design space defined by process models clearly provides greater flexibility in that it allows access to process conditions for time, temperature, and pH which would be excluded by registration of the fixed cuboid design space. Use of these models requires that temperature is controlled isothermally throughout.

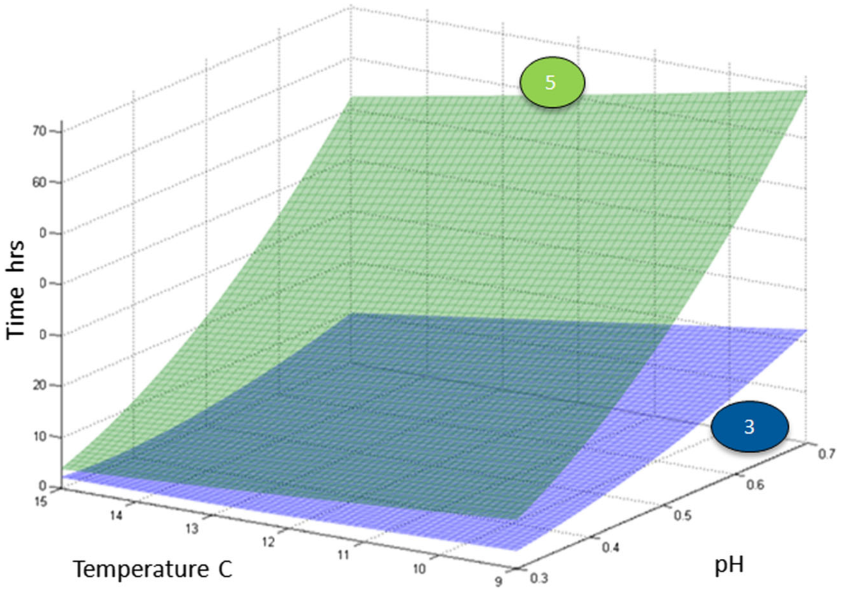


Fig. 11 Visualization of process models for ethyl impurity 3 and acetonide 5

Model Verification and Scalability For models developed through experimentation at small scale, consideration should be given to the applicability of the model to commercial scale. It is essential to evaluate the potential for elements such as mass transfer or equipment sensitivity to impact the validity of the model developed in the laboratory as the scale is increased. In this case, the risk may be assessed by consideration that both the acetonide 3 and the Drug Substance X 4 are in solution throughout the process. Additionally, the reaction conditions selected control the process such that, even at the fastest conditions selected (of low pH and high temperature) the reaction time is several hours. Hence, mass transfer effects do not pose a risk to the scale-up, and the model should hold across a wide range of scales and equipment.

Control Strategy for the Commercial Process For commercial manufacture, it is important to consider which control strategy offers acceptable flexibility, and to consider how the control strategy might be implemented on the factory floor, and what considerations of the manufacturing site's PQS are important. The process understanding, exemplified by data similar to that presented in this case study, was presented in the regulatory submission in Section S2.6. The process understanding was used to justify a control strategy which included fixed ranges for 6.0-M HCl amount and temperature. A control strategy which included no defined range for the reaction time was accepted, based on the data provided and the registration of an in-process test for level of the acetonide 3 and the ethyl impurity 5. Such a control strategy is considerably more flexible than fixed ranges for the CPPs. Registration of a variable range for time, or of the process models was also considered, and it is believed that such approaches would also have been justifiable and acceptable to regulatory authorities, based on the process understanding developed.

Registration of control strategies defined by a design space has been a challenge in implementing ICH Q11. One of the root causes of the challenge, is different viewpoints from regulators as to what degree of assurance of control of CQAs the design space should provide, and what data at laboratory and commercial scale is needed for the design space claimed by the applicant to be approved. The data presented in this case study should be appropriate to justify a low/medium impact design space. Impact in this case, refers to the role of the design space in the overall control strategy, which includes testing of the CQAs 3 and 5 as part of drug substance release.

Table 4 Comparison of minimum and maximum reaction times for a variety of pH and temperature conditions

		Temp (°C)			
		9	11	13	15
6-M HCl amount (pH)	1.3 vols (pH 0.3)	3–14	3–9	2–7	2–5
	0.6 vols (pH 0.6)	13–35	11–23	7–17	4–16
	0.8 vols (pH 0.9)	20–43	24–50	30–67	36–78

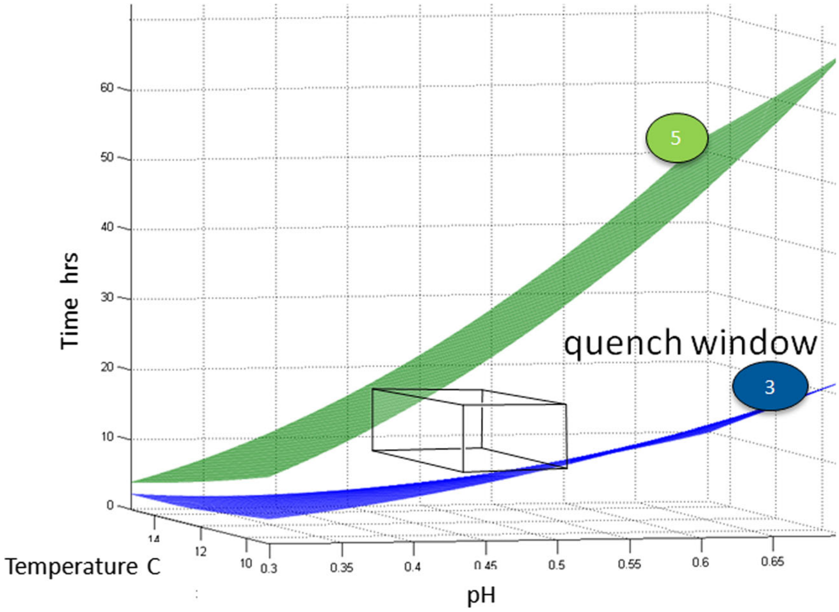


Fig. 12 Comparison of the design space defined by fixed parameter ranges with that available based on the models

Role of Process Understanding in Facilitating Future Changes

The comprehensive mechanistic and DoE studies undertaken give confidence that the impact of processing conditions on API quality are well understood and is therefore of benefit to patients. ICH Q11 states that: "*greater understanding of the drug substance and its manufacturing process can create the basis for more flexible regulatory approaches.*"

To that end, it is useful to consider what potential changes across the product lifecycle of Drug Substance X could be facilitated, based on the process understanding developed. For example:

- The models justify alternative control strategies, such as the removal of the end product tests for the CQAs acetonide 3 and ethyl impurity 4. In such cases the design space and its underlying models would become high impact, and additional consideration of verification and lifecycle maintenance be required.
- Basic mechanistic and engineering principles support that the models for a slow, homogeneous, isothermal reaction should be scale and equipment independent and the data generated justify that changes to the scale or equipment and site of manufacture should present a very low risk. Hence, this enhanced development approach justified a wide range of manufacturing scales, and could be used to support a product specific lifecycle plan which includes management of changes to the scale under the manufacturing site's PQS without notification to regulatory authorities.

Simple considerations such as these, related to the regulatory requirements supporting changes across the lifecycle, will facilitate future changes and help reduce costs and complexity across the lifecycle, without impacting patient safety.

Case Study 5: Development of a Control Strategy for a Final Intermediate to Enable Impurities Control [18]

Summary

In accordance with the ICH guidelines, CQAs for drug substance are established based on the QTPP of the drug product followed by quality attributes of the intermediates and starting materials. This case study describes the reaction of a final intermediate which contains six process-related potential CQA impurities which were considered during the development of the control strategy.

The approach to control critical CQA impurities is rooted in a detailed understanding of the reaction mechanism as well as the purge capability during workup and crystallization. This knowledge enabled the identification of parameters that could impact the impurity profile of the drug substance. The effect of

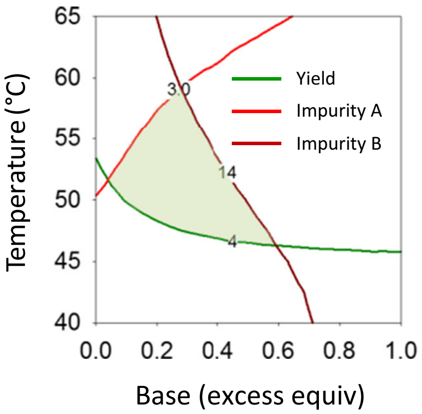


Fig. 13 Combined contour plots of interest for the response surfaces of yield, Impurity A and Impurity B

the identified parameters was evaluated based on prior experience and DoE results for the coupling reaction — deprotonation reaction hold time, reaction temperature, excess equivalents of base, and equivalents of residual water, had the highest impact on the formation of the CQA impurities.

Mechanistic studies of the coupling reaction were carried out to understand the consumption of the input materials with respect to product and impurity formation as well as to build a mechanistic model that could reliably predict kinetic profiles for these species. The model was used to determine process conditions that would facilitate the control of the impurities within acceptable limits while ensuring quality (Impurity A) and maximizing reaction yields (Impurity B) (Fig. 13). Two different methods were considered to explore the design space: a fixed reaction age approach (time for the reaction completion), and a variable reaction age approach with fixed post-reaction time. The fixed reaction age approach managed reaction age variability by controlling the levels of impurities A and B within a wide time range (22–30 h). Thus, maintaining fixed parameters at their limit values afforded contours that enclosed the acceptable operating space shown in Fig. 14.

The variable reaction age approach with fixed post-reaction time was defined with the provision that the reaction would be continuously monitored for completion. While this approach addressed age variability, the reaction hold-time post completion could become a possible failure mode since, at a given reaction temperature, prolonged times might lead to impurity levels that exceed the established in-process limits. The variable reaction age approach was made possible by the development of a Raman method that provided in-situ reaction monitoring with the appropriate degree of accuracy and was confirmed using the HPLC.

The combination of a variable reaction age with in-situ monitoring significantly broadened the ranges of temperature and excess equivalents of base which can be accessed, thereby delivering greater flexibility (see Fig. 15). This approach enabled a robust process that could be more readily applied during commercial manufacturing and supported during lifecycle.

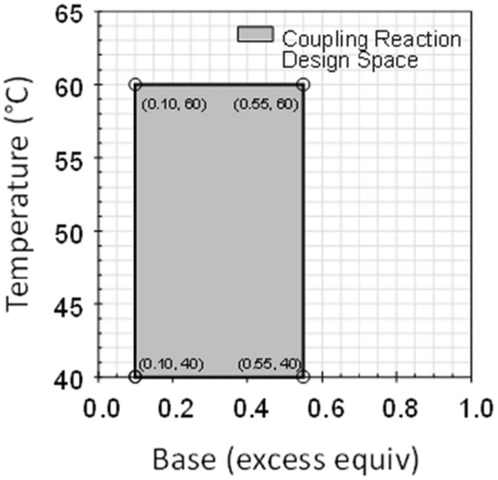


Fig. 14 Design space accessible using variable reaction age

Conclusions The defined control strategy was developed utilizing the basis of ICH Q8 (R2) together with the principles in ICH Q11. A risk-based approach (ICH Q9) was used to define the CQAs and the process parameters for the step. Based on mechanistic understanding of impurity formation, a kinetic model was developed (ICH Q10) and used to guide the development of the design space. This led to a robust and cost-effective process that ensures drug substance quality and yield through control of the CPPs of coupling reaction temperature and excess equivalent of base. Based on the kinetic models developed, more flexible, broader ranges for the CPPs were introduced through control of the in situ reaction monitoring. The above information was provided in the dossier and received successful approval from all regulatory authorities.

Conclusions

The enhanced development approaches exemplified here have been used to develop control strategies which have been applied to deliver greater flexibility in various ways. It is noteworthy that the science which underpins the development could be used to support various control strategies to deliver greater flexibility to manufacturers, and which could be used to support product specific lifecycle plans that include elements such as changes to the manufacturing site or scale.

Simple considerations such as these, related to the regulatory requirements supporting changes across the lifecycle, can facilitate future changes and help reduce costs and complexity across the lifecycle, without impacting patient safety. Such factors are key considerations for companies developing manufacturing processes and their registration and control strategies, and reflect a clear benefit of an enhanced QBD development approach.

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References

Case Study 1 & 2

1. ICH Q11 Q9 Guidelines.

Case Study 2

2. Seibert K, Sethuraman S, Mitchell J, Griffiths K, McGarvey B. The use of routine process capability for the determination of process

parameter criticality in small-molecule API synthesis: *J.* Pharm Innov. 2008;3:105–12.

3. Mitchell J, Abhinava K, Griffiths K, McGarvey B, Seibert K, Sethuraman S. Unit operations characterization using historical manufacturing performance. Ind Eng Chem Res. 2008;47:6612–21.

Case Study 3

4. Am Ende D, Clifford P, DeAntonis D, Santamaria C, Brenek S. Preparation of grignard reactants: ftir and calorimetric investigation for safe scale up. Org. Proc. Res. Dev. 1999;3:319–29.
5. Caygill G, Zanfir M, Gavriilidis A. Scalable reactor design for pharmaceuticals and fine chemicals production. 1: potential scale-up obstacles. Org. Proc. Res. Dev. 2006;10:539–52.
6. Figueroa I, Vaidyaraman S, Viswanath S. Model-based scale-up and design space determination for a batch reactive distillation with a dean-stark trap. Org. Proc. Res. Dev. 2013;17:1300–10.
7. Gonzalez-Bobes F, Kopp N, Li L, Deerberg J, Sharma P, Leung S, et al. Scale-up of azide chemistry: a case study. Org. Proc. Res. Dev. 2012;16:2051–7.
8. Hoekstra L, Vonk P, Hulshof L. Modeling the scale-up of contact drying processes. Org. Proc. Res. Dev. 2006;10(3):409–16.
9. Tangler A, Szabados E. Overcoming problems at elaboration and scale-up of liquid-phase Pd/C mediated catalytic hydrogenations in pharmaceutical production. Org. Process Res. Dev. 2016;20:1246–51.
10. Anderson N. Practical use of continuous processing in developing and scaling up laboratory processes. Org. Proc. Res. Dev. 2001;5:613–21.
11. Johnson M, May S, Calvin J, Remacle J, Stout J, Diseroad W, et al. Development and scale-up of a continuous, high-pressure, asymmetric hydrogenation reaction, workup, and isolation. Org. Proc. Res. Dev. 2012;16:1017–38.
12. Polster C, Cole K, Burcham C, Campbell B, Frederick A, Hansen M, et al. Pilot-scale continuous production of LY2888721: amide formation and reactive crystallization. Org Proc Res Dev. 2014;18:1295–309.
13. Zaborenko N, Lynder R, Braden T, Campbell B, Hansen M, Johnson M. Development of pilot-scale continuous production of an LY2886721 starting material by packed-bed hydrogenolysis. Org. Proc. Res. Dev. 2015;19:1231–43.
14. Food and Drug Administration Code of Federal Regulations, Tittle 21, Volume 4 (21CFR210.3).
15. Thomson N, Singer R, Seibert K, Luciani C, Srivastava S, Kiesman W, et al. Case studies in development of drug substance control strategy. Org. Proc. Res. Dev. 2015;19:935–48.
16. Rathore A, Velayudhan A. Guidelines for optimization and scale-up in preparative chromatography. BioPharm International. 2003;16:34–42.
17. García-Muñoz S, Luciani C, Vaidyaraman S, Seibert K. Definition of design spaces using mechanistic models and geometric projections of probability maps. Org. Proc. Res. Dev. 2015;19:1012–23.

Case Study 5

18. The development of a control strategy for a final intermediate towards the preparation of a drug substance is described in Org. Process Res.Dev.2016, 20, 1781–1791 (published on October 7, 2016).