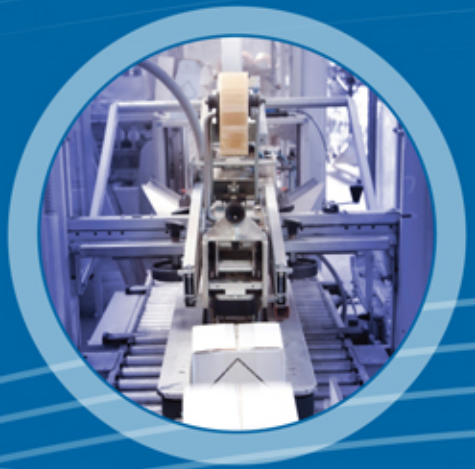
Connecting People, Science and Regulation

# Case Study 2: Development and Verification of Design Space

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# Case Study Team

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# Case Study 2: Overview

- Introduction to Case Study
- Overview of Product A
- Discussion Topics
  1. Development of Design Space
  2. Scale-up and Design Space Verification
  3. Presentation of Design Space in the Submission
- Topics recommended for further discussion

# Introduction to Product A Design Space Case Study

- Process capability metrics for recent QbD products show improved robustness compared to older, ‘more traditional’ products

- But preparation of recent ‘QbD’ applications required significant greater resources – and generated more queries

- How can the inclusion of enhanced development information in a submission be optimised and the design space concept be utilised more effectively?

# Overview of Product A

- Indication
  - Advanced renal-cell carcinoma
- Product A Dosage Form
  - Immediate-release, film coated tablets
  - Conventional dry granulation manufacturing process
- Product A Drug Substance
  - 6 stage synthesis from 3 starting materials
    - Includes 5 chemical transformations, 4 isolations, 2 crystallizations
  - Various crystal forms identified
  - Single crystal form (non-hygroscopic) commercialised

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# Discussion Topic 1 - Developing a Design Space

Development Approach for Product A (DS and DP):

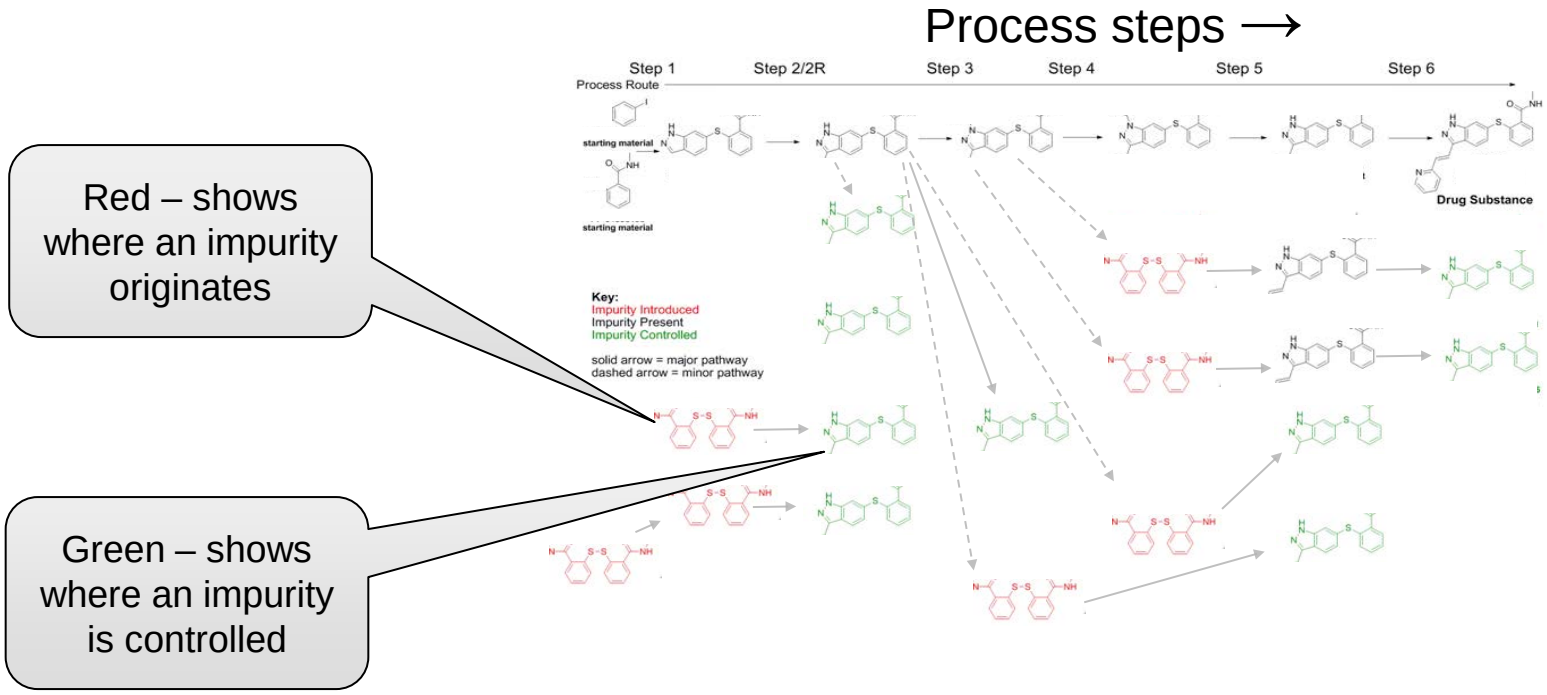
- Understand what needs to be delivered to the patient by the drug product and drug substance (QTPP and CQAs)
- Understand what acceptance criteria are needed of CQAs to deliver safety and efficacy
- Understand aspects of the input materials and process that build in critical elements of quality
- Understand links between process parameters, material inputs and CQAs – risk assessment and experimentation
- Understand important interactions between parameters and inputs - experimentation
- Determine the manufacturing conditions that can deliver the CQAs to appropriate quality (PARs or Design Space)

Typical approach following QbD principles

# Discussion Topic 1 - Developing a Design Space

## Developing a Design Space for the Drug Substance

- Risk Assessment
  - CQAs identified include Palladium (catalyst) and Impurities
  - Impurity mapping grids show where impurities are formed and controlled:



# Discussion Topic 1 - Developing a Design Space

- Risk Assessment continued:
  - Process steps ranked for importance in delivering CQAs
  - Focus on ‘control gates’ for impurities e.g. isolations and bond-forming steps:
    - Step 6 and milling
    - Step 5 crystallization and Step 4 reaction
    - Step 2R re-crystallization

    } Highest ranked

    - Steps 1 and 2

    } Low ranked because impurities do not propagate through process
- Design space
  - Design space developed for each process step and combined to give design space for whole process
  - Preliminary trends on impact of PPs on CQAs determined from risk assessment + prior knowledge + experiments
  - For all processing steps the impact of mixing was examined using a variety of equipment configurations
  - Highest risk PPs were studied using multivariate DoEs
  - Design space founded on parameters with most influence on CQAs

# Discussion Topic 1 - Developing a Design Space

**Example: Design Space for Step 5 Crystallization**

- Step 5
  - Polishing filtration of step 4 mixture
  - Deprotection of acyl group and removal of Pd
  - Crystallization  by addition of anti-solvent
  - Reslurry
- Preliminary experiments showed various parameters had no impact e.g.
  - Cooling rate
  - Deprotection time and temperature

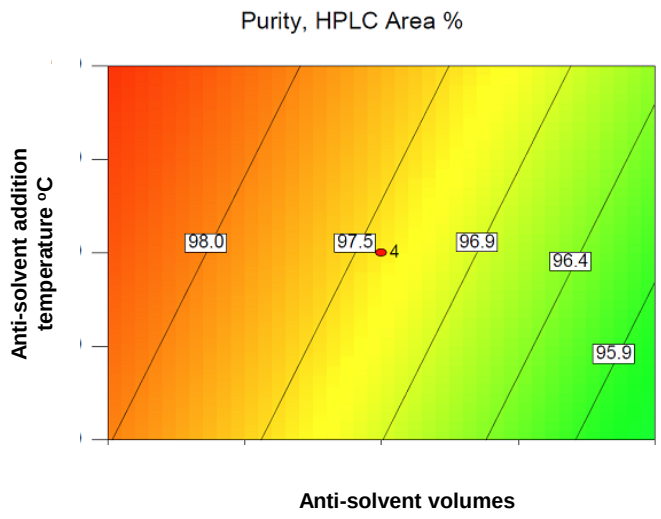
# Discussion Topic 1 - Developing a Design Space

- Step 5 Crystallization DoE
  - Parameters selected based on prior experimental work e.g.
    - Order of addition
    - Anti-solvent temperature
    - Anti-solvent quantity
    - Quantity of acyl group deprotection agent
  - Focus on impurities:
    - PF-039xxxxx
    - PF-033xxxxx
    - Pd
  - Results
    - Anti-solvent quantity had biggest effect, followed by anti-solvent temperature
    - PF-039xxxxx not impacted by any parameters
    - Two parameters affected yield but not quality

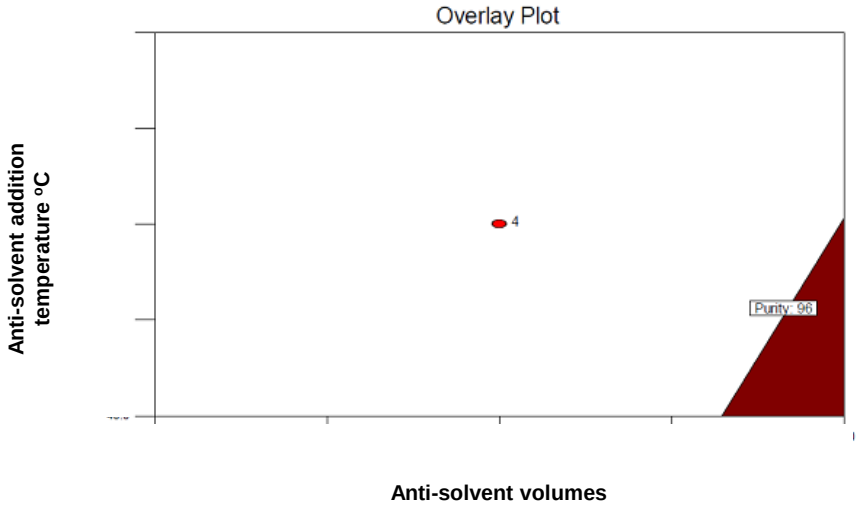
# Discussion Topic 1 - Developing a Design Space

- Predicting the optimal region for Step 5 crystallization
  - Statistical model derived from experimental data
  - Additional confirmatory experiments confirm model
  - Design space to achieve >96% purity of crude drug substance; after reslurry >99% purity achieved

Statistical model: Contour plot of anti-solvent temperature and volume for crystallization




Design space: Overlay plot showing region for >96% purity of crude drug substance (in white)



# Discussion Topic 1 - Developing a Design Space

- A question during our discussions:
  - 'Why did you want a design space?'
- Discussion about development and regulatory submission strategies e.g.
  - Is a design space a 'natural outcome' of an enhanced development including multi-variate experimentation?
  - Is a design space a specific 'regulatory approval objective' because the applicant has identified a need for flexibility in a particular part of the process?
    - During the development stage of the lifecycle, companies may not be able to identify all areas where 'operational flexibility' may be needed by the manufacturing organization

# Discussion Topic 1 - Developing a Design Space

- 'Would the type of product, dosage form, drug substance characteristics etc. affect the development of a design space?'
  - The general approach to design space development can be applied to any kind of product
  - Different design spaces can be developed but all will be founded on scientific understanding of multivariate combination and interactions of parameters and attributes
  - Industry experience to date suggests that design spaces for more complex products (e.g. biopharmaceuticals) may be harder to get approved

# Discussion Topic 1 - Developing a Design Space

- ‘Best practice’ recommendations
  - When should an Applicant request approval of a Design Space?
  - Applicant should carefully evaluate what operational flexibility they need, and the complexity of the product, when considering design space vs PARs
  - Applicants should consider the role of the design space in assuring quality within the control strategy (see Case Study 5 ‘Control Strategy’)

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# Discussion Topic 2: Scale-up and Design Space Verification

- Issue
  - Design spaces are often developed at small scale and it is necessary to demonstrate within the design space boundaries that scale-up effects are under control and do not adversely affect expected product quality at commercial scale
  - How can the design space be verified – at commercial scale - using a science- and risk-based approach?

# Discussion Topic 2: Scale-up and Design Space Verification

- Observations/Learnings:
  - Day 120 Question:
    - The number of batches and batch sizes employed in all purge studies used in justifications of skip testing of palladium, solvents and related impurities should be provided.
  - Agreement on importance of understanding and managing the impact of change of scale on the manufacturing process and product quality whether a design space or PARs
  - Purge understanding was developed using small-scale spiking experiments at worst case impurity levels (developed from process understanding)
    - Acceptance criteria for controls of Pd levels were derived experimentally
    - The control strategy includes additional assurance of quality (Pd tested at Step 5) - testing is independent of scale

# Discussion Topic 2: Scale-up and Design Space Verification

- Observations/Learnings
  - Day 120 Question: The results of any laboratory- or pilot scale experiments (i.e. the design space) should be verified by a suitable set of experiments on full production scale.
  - Design Space Verification Protocol provided
    - Described actions to be taken to confirm that areas within the DSp consistently meet and maintain API quality
    - Documented and managed in the site Change Management system
    - Filed in Regional section of Module 3
  - Agreed data generated in accordance with protocol would not need to be submitted, but may be requested during an inspection
  - Assessors noted that scale and equipment change should not be in scope and such changes would need Variations to be filed
    - Protocol should *"encompass the spirit of process validation"*

# Discussion Topic 2: Scale-up and Design Space Verification

## Key Elements of Drug Substance DSp Verification Protocol:

1. Initial verification of the NORs
   - Encompassing clinical, stability and PV batches
2. Change management
   - Proposed general science- and risk-based assessment approach to evaluate change for impact on control strategy and API quality
   - Considerations include: Criticality of process parameters impacted; Are multiple changes being made concurrently?; Degree of movement within Design Space; Potential impact on CQAs; Potential impact on stability; Equivalence of API in Drug Product
3. Design Space Verification specific for Product A
   - Post-approval changes to PPs away from NOR process, to area of higher or unknown risk will include re-verification at commercial scale of the proposed new operating area within the Design Space
   - Selection of appropriate testing (may include additional monitoring/testing)

# Discussion Topic 2: Scale-up and Design Space Verification

| EMA –FDA Q&A 24 Oct. 2013 | Submitted Protocol (for API, 2012) |
|---|---|
| 'Principles': | |
| • Movement within DSp may pose higher/unknown risks due to potential scale-up effects and/or model assumptions<br>• Not necessarily complete at time of submission, should occur over product and process lifecycle<br>• Initial verification solely or near target operating ranges is possible<br>• Not necessary to repeat small scale experiments<br>• Not necessary to verify entire design space<br>• Not necessary to identify edge of failure | • Actions to be taken to confirm that areas within DSp meet control strategy<br>• Initial verification using clinical, registration stability and process validation batches<br>• Initial verification of NORs |
| 'Approach': | |
| • Guided by risk assessment<br>• Consider potential impact to product quality<br>• Consider control strategy detection of failures<br>• Additional non-routine monitoring of QAs or PPs? | • Structured risk assessment to evaluate impact on quality, CQAs, CPPs and control strategy<br>• Equivalence studies, as needed<br>• Further lab scale experiments, if needed<br>• Further assessment of stability, if needed<br>• Additional monitoring of CQAs and CPPs, if needed |

# Discussion Topic 2: Scale-up and Design Space Verification

| EMA –FDA Q&A 24 Oct. 2013 | Submitted protocol (for API, 2012) |
|---|---|
| Protocol to include: | |
| • List of scale-dependent parameters<br>• Definition of the potential scale-up risks to the CQAs<br>• Discussion of whether the control strategy can address risks<br>• Description of any additional controls | • List of CPPs and impacted CQAs<br>• Limited information*<br>• Limited information*<br>• Analytical testing plans defined include additional testing |
| Regulatory Aspects | |
| • Location for Protocol: 3.2.R (EU)<br>• Data managed and documented in site change management system (EU) | • Included in 3.2.R<br>• Data managed and documented in site quality system |

* Agencies may require additional information in these areas for protocols submitted today

# Discussion Topic 2: Scale-up and Design Space Verification

Current expectations on specific information in a Design Space Verification Protocol

- Protocol is not expected to be exhaustive - Format and content is still under discussion
  - Not every possible change should be covered
- For movements in relevant directions in a given Design Space, indicate failure mode, effect of failure and control strategy
  - e.g. movements from NORs towards identified ‘edge of failure’ could be matters of concern, requiring additional monitoring
  - Other changes (movements?), appropriately covered by the control strategy, do not require specific discussion
- Additional monitoring
  - May be needed, depending on magnitude of movement, established interactions and probability of failure (i.e. is linked to process understanding)
  - Describe what additional monitoring is planned when given parameters are changed outside the NOR within the Design Space
  - Additional monitoring/testing could be specific for the failure mode

# Discussion Topic 2: Scale-up and Design Space Verification

- Best Practice recommendation
  - The DSp verification protocol submitted (in 2012) was largely consistent with recent EMA-FDA Guidance (Q&A; 24 Oct 2013); additional details may be required

- Topic for further discussion
  - Is potential risk from the development of the Design Space from only small-scale studies mitigated by the control strategy applied?

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# Discussion Topic 3: Presentation of Design Space

- Dialogue during Case Study discussions:
  - 'Were additional experiments done to answer questions from the dossier review?
  - 'No additional experimental work was conducted to answer the questions; data was already available'
  - Conclusion: Presentation of Design Space information was a critical factor in the review of this dossier and to questions asked
- Issue: Where and how in the CTD should the design space information be presented?
  - Are these presentations appropriate for a manufacturing process description in CTD sections S.2.2 or P.3.3? For a Master Batch Record?

# Discussion Topic 3: Presentation of Design Space

- Existing guidance on presentation of Design Space
  - Examples for presentation in ICH Q8(R2)
  - Further elaboration in the ‘Points to Consider’ document
  - Does including ‘non-critical process parameters’ in regulatory manufacturing process descriptions increase the post-approval change burden, even when a Design Space is used?

C. Presentations of design space

**Example 1:** Response graphs for dissolution are depicted as a surface plot (Figure 1a) and a contour plot (Figure 1b). Parameters 1 and 2 are factors of a granulation operation that affect the dissolution rate of a tablet (e.g., excipient attribute, water amount, granule size.)

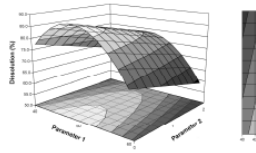


Figure 1a: Response surface plot of dissolution as a function of two parameters of a granulation operation. Dissolution above 80% is desired.

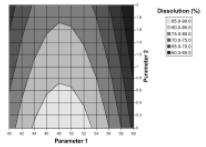


Figure 1b: Contour plot of dissolution from example 1a.

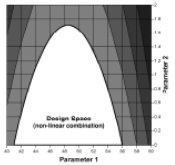


Figure 1c: Design space for granulation parameters, defined by a non-linear combination of their ranges, that delivers satisfactory dissolution (i.e., >80%).

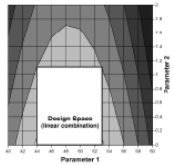
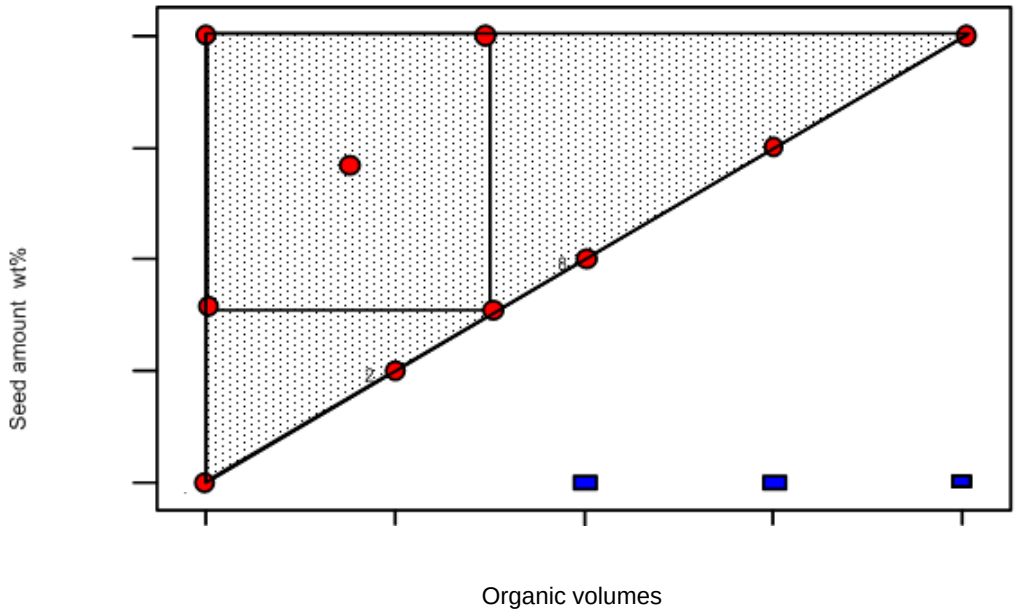


Figure 1d: Design space for granulation parameters, defined by a linear combination of their ranges, that delivers satisfactory dissolution (i.e., >80%).

‘Inclusion of a clear statement of the proposed design space and the location of the filed information (hyperlinked, where possible) in regulatory submissions should be considered to facilitate the regulatory process.‘(PtC)

# Discussion Topic 3: Presentation of Design Space

- Drug Substance Design Space for crystallization at Step 6 presented in 2.3.S.2.6




*The red symbols indicate experimental systems that result in isolation of form alone, while blue symbols indicate experimental systems that isolated a mixture of form and form The grey region depicts the optimal operating space for step 6.

# Discussion Topic 3: Presentation of Design Space

## Drug Substance Design Space Summary from QOS 2.3.S.2.6:

Attempt to focus on critical/key attributes/ parameters and differentiate parameters

| Parameter | Operational Boundaries | Target or Normal Operating Range | Criticality (critical, key or non-critical) |
|---|---|---|---|
| Total quantity of XXX | | | Non-critical |
| Quantity of MMMM NNNNN in ZZZZ | | | Non-critical |
| **Temperature of substep** | | | Non-critical |
| Quantity of ZZZZ | | | Non-critical |
| Temperature of ZZZZ during addition of XXX/YYY mixture | | | Non-critical |
| Temperature of TTTTT | | | Non-critical |
| Time exposed to LLLL before and after crystallization | | | Non-critical |
| Stir time of GGGGG prior to filtration | | | Non-critical |
| Quantity of ZZZZ for reslurry | | | Non-critical |
| Temperature of reslurry | | | Non-critical |
| Hold time | | | Non-critical |
| Temperature after TTTTT | | | Key |
| Hold time | | | Key |
| Ratio of XXX, YYY and ZZZZ volumes | | | Key |
| **Time for substep** | | | Key |
| **Temperature of substep** | | | Key |
| Quantity of YYY | | | Critical |
| Amount of SSSSS | | | Critical |
| Quality of axitinib form | see Section 3.2.S.4.1. Specification for Drug Substance | See Table 2.3.S.2-16 | Critical Quality Attributes |

Meq = molar equivalents, NMT = not more than, NLT = not less than

**Note: Do not use 'Key' to differentiate criticality of parameters**

Non-critical parameters were not incorporated in the regulatory process description in 3.2.S.2.2

Design Space expressed as simple ranges in this summary and these ranges incorporated in the regulatory process description in 3.2.S.2.2

Note:
This summary is for one unit operation but the proposed Design Space encompassed several unit operations

# Discussion Topic 3: Presentation of Design Space

- What was presented in the dossier:
  - Quality Overall Summary 2.3:
    - Design space  development work presented in process development sections S.2.6 and P.2
      - Additional summaries of risk assessments could have been helpful to include
    - Ranges for critical and key* process parameters given in the regulatory process descriptions in S.2.2 and P.3.3
  - But the words ‘Design Space’ did not appear in the Descriptions of the Manufacturing Processes for drug substance or drug product in 3.2.S.2.2 or 3.2.P.3.3

***Note: Do not use ‘Key’ to differentiate criticality of parameters**

# Discussion Topic 3: Presentation of Design Space

- Enhanced knowledge and appropriate commitments:
  - Day 120 question: If DSps are used this should be evident from the manufacturing description and the DSps should be included together with the values applied for non-critical process parameters.
  - Day 120 question: Information about the parameters and values not included in the DoE for the Step 2 should be reported.
  - **Summary of the Applicant's Response:** All parameters in steps 1-2 are non-critical due to a recrystallization at step 2R which controls all impurities efficiently and confirmation of the control of impurities through analytical testing of recrystallized AG-02xxxx (Section 3.2.S.2.4. Control of Critical Steps and Intermediates).
  - **Assessment of the Applicant's response:** The response is considered acceptable. It expected that the values for the parameters not included in the DoE have been held constant at their target values.

# Discussion Topic 3: Presentation of Design Space

- ‘Best Practice’ Recommendations
  - The regulatory process descriptions in sections S.2.2 and P.3.3 should be sufficiently detailed and include all relevant process parameters linked to CQAs
    - Ranges or target values should be stated
    - Some non-CPPs may need to be included
  - The regulatory process descriptions in sections S.2.2 and P.3.3 should explicitly state where a design space is applied and interactions between parameters
  - Do not use ‘Key’ to differentiate criticality of parameters
  - Note: Presentation of in-process controls and design space is discussed in Case Study 5 ‘Control Strategy’

# Topics Recommended for Further Discussion

- How can parameters with lesser impact be differentiated from Critical Process Parameters to avoid increasing the regulatory change burden?
  - Parameters do not affect a CQA equally – some have more effect than others
  - Can the regulatory framework accommodate differences between CPPs vs non-CPPs for post-approval changes?

- Can a consideration of the role of the design space in the control strategy facilitate the assessment and agreement on information to be included in the process description (subject to change by Variation)?