



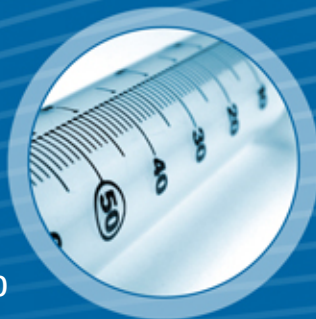
Connecting People, Science and Regulation®

Case Study 1: Risk Assessment and Lifecycle Management Learning

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Case Study 1: Overview

- Team
- Introduction to Case Study
 - Overview of Product A & B
 - Review outcomes
- Discussion Topics
 1. Risk Assessment
 2. Lifecycle Management



Thanks to the Team

AstraZeneca

- Frank Montgomery (Reg)
- Tove Illing (Reg)
- Dave Holt (Pharm Dev)
- Ali Grinell (Reg)

Additional support

- John Gilday (Pharm Dev)
- Gavin Reynolds (Pharm Dev)
- Bob Timko (Reg)

Regulators

- Olvia Lake (EU Quality Assessor)
- Jobst Limberg (EU Quality Assessor, QWP Rep)
- Emil Schwan (EU Inspector)
- Virve Reiman-Suijkerbuijk (EU Inspector)



Introduction

- Case study will describe learning from 2 Approved MAAs
- Both products are small molecule, immediate release tablets
 - Product A (BCS IV), Product B (BCS II)

What were we trying to achieve?

- Product / Process Robustness
 - Understand factors impacting clinical performance and relevant measures
 - Robust product & process Control Strategies through scientific understanding
- To learn about Quality by Design
 - AZ Pilot / Test Case Products (accepted into FDA Pilot program)
 - Understand if possible to reduce need for post approval changes through application of an enhanced approach



Product A & B Approaches

- Different interpretation of Design Space By AZ of ICH Q8 caused confusion
 - Our perception was that this complicated the review

Product A

- Used as a test case to understand application of alternative control strategies
 - This is a robust, high quality product that allowed this approach
 - Less reliance on end product testing
- Complex holistic design space submitted for both API & Product
 - Lots of controls replaced by alternative non traditional approaches
 - Used material intermediate attributes as inputs to define the design space reduced parametric descriptions

Product B

- More traditional overall control strategy vs Product A
 - Discreet design space proposals for drug substance & product manufacture
 - Parametric control explicit for Product B drug product
 - Extrapolated upper scale limit

Similarities

- Similar approaches adopted for dissolution and specification
- Similar levels of data submitted in MAAs to support Control Strategy



Product A & B Review Outcomes (1)

Product B (2010)

- Consistent with previous non-QbD reviews
 - Some explanation of Design Space (DSp) proposals but no significant additional data requests

Product A (2011)

- Lots of Questions & Large data package required to support proposals
 - Huge challenge to respond in time available and presumably to review
 - Followed very closely ICH Points To Consider (PTC) “Level of documentation in Enhanced (QbD) Regulatory Submissions”
 - Negatively impacted AZ perspective on business case for enhanced submissions

Learning

- Expectations have adapted since this review
 - Large data requests and extensive Q&A would not be expected now for same dossier

Discussion Point

- **Is clarification or moderation of “Points to Consider” needed?**



Product A Review Outcomes (2)

Accepted

Wide ranges for Process Parameters when fully supported in DoE.

Spec limits based on process capability for all Intermediates and Starting Materials including GTI controls

No testing of Inter 1 & Crude API

Partial Acceptance

Reduced API testing replaced by up stream controls PGI controls, morphology, water content, some solvents

SM 1

Non-Isolated Inter 1

Non-Isolated Inter 2

Isolated Inter 1

Isolated Inter 2

Crude API

Pure API

SM 2

SM 3

Not Accepted

Reduced description of process parameters (PP) esp. in early stages

Required to include narrow ranges on non-critical PP (not included in DoEs)

Single sided PP ranges

Robust Intermediate spec replacing PP



Regional Review Outcomes

- Product A NDA & Product B NDA/MAA had relatively similar reviews
- Product A MAA & Product B JNDA significant increase in data expectations
 - Followed very closely ICH points to consider “Level of documentation in Enhanced (QbD) Regulatory Submissions”

Regional Differences (EU /US/Jp/ Can)

- Complex control strategies and regional interpretations unsurprisingly led to range outcomes from different agencies
 - Control of clinical quality and dissolution philosophy is different and resulted in different dissolution specifications for both products and method for Product A
 - Sunset clauses vs. annual testing Product A



Discussion Topic 1: Risk Assessment (RA)

REVIEW OUTCOME & LEARNING FOR FUTURE



RA Methodology Used by AZ

- Inputs to Quality Risk Assessment
 - QTPP, Potential CQAs
- Risk Assessment Sessions based on FMECA methodology (ICHQ9)
 - Trained facilitators, multi-skilled teams, quantitative scoring
- Documentation of Risk Assessments
 - Well documented, peer review and approved (available for PAI)
 - A number of risk assessment processes may performed during development
- Risk assessment drives development work
 - Risks are prioritised based on risk score (don't necessarily 'do nothing' for 'low' risks)
- Communication in regulatory submissions
 - Challenge to translate the raw QRA outcomes into an appropriate summary
 - Summary information could lead to misinterpretation at review



Risk Assessment Submitted by AZ in MAA

What did we submit for Product A & Product B?

Traffic lights representations were used to try and provide a high level summary of the evolution risk and link to control strategy through submission

- A number of questions related to risk assessment methodology and detail behind the 'traffic light' approach
- Responses provided context and process for RA
- More clearly referenced relevant areas of the submission to justify risk levels

Initial Risk Assessment

CQAs	Dry mix	Wet granulation	Wet mass de-lumping	Drying	Dry milling	Blending	Comp-ression	Coating	Packing
Assay	Low	Low	Low	Low	Low	Low	Low	Low	Low
Degradation products	Low	Low	Low	Low	Low	Low	Low	Low	Low
Uniformity of dosage unit	Low	Low	Low	Low	Low	Low	Low	Low	Low
Dissolution	Low	Medium	Low	Medium	Medium	Medium	Medium	Low	Low
Microbiology	Low	Medium	Medium	Medium	Low	Low	Low	Low	Low
Non-CQAs									
Appearance, eg, tablet picking	Low	High	Medium	Low	Medium	Medium	Medium	Low	Low
Hardness	Low	High	Medium	Low	Medium	Medium	Medium	Low	Low
Friability	Low	Medium	Medium	Low	Medium	Medium	Medium	Low	Low

After definition of the overall design space and associated control strategy



Product CQAs	Dry mix	Wet granulation	Wet mass de-lumping	Drying	Dry milling	Blending	Comp-ression	Coating	Packing
Assay	Low	Low	Low	Low	Low	Low	Low	Low	Low
Degradation products	Low	Low	Low	Low	Low	Low	Low	Low	Low
Uniformity of dosage unit	Low	Low	Low	Low	Low	Low	Low	Low	Low
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Appearance, eg, tablet picking	Low	Low	Low	Low	Low	Low	Low	Low	Low
Hardness	Low	Low	Low	Low	Low	Low	Low	Low	Low
Friability	Low	Low	Low	Low	Low	Low	Low	Low	Low



RA representation

Best Practice Proposal (Case Study Team)

Company view based on discussion with Regulators in CASE Study Team

- Table, with highest failure modes in each category and quantitative scores

CQAs	Raw Materials	Dry Mix	Wet Granulation	Drying	...
Assay	None	None	- sticking (40)	- loss of fines (18)	
Degradation products	None	None	- hold time (36)	- temperature (16) - sampling for LOD (24)	
Uniformity of dosage unit	- physical properties (64)	- mixing time/speed (12)	- extreme granule size (60)	None	
Dissolution	- particle size (32) - disintegrant FRC (60)	None	- granule densification (80)	None	
Microbiology	None	None	- hold time (36)	- sampling for LOD (24)	

- Followed by a discussion/justification on identified failure modes and scores (and perhaps absence of failure modes in some areas).

CQA	Process Step	Failure Mode	P	S	D	RPN	Justification
Dissolution	Wet Granulation	Granule Densification	5	4	4	80	This is a highly probably failure mode prior to developing process understanding. Would detect effect at end product testing, which would require an investigation.



Link risk profile to control strategy

Best Practice Proposal (Case Study Team)

- Table is showing the links between CQAs & control strategy (Material Attributes & Process Parameters)

CQAs	Raw Materials	Dry Mix	Wet Granulation	Drying	...
Assay	Quantitative composition	None	None	None	
Degradation products	None	None	None	Inlet air <70°C LOD <2%	
Uniformity of dosage unit	Qualitative composition	Mixing time: 5 minutes Mixing speed: 3-6 m/s	Water: 35-40% Time: 6-8 minutes	None	
Dissolution	Particle size specification	None	Water: 35-40% Time: 6-8 minutes	None	
Microbiology	None	None	None	LOD <2%	

- More detail, showing how control strategy mitigates risk:

CQA	Process Step	Failure Mode	P	S	D	RPN	Control Strategy Elements	Justification
Dissolution	Wet Granulation	Granule Densification	1	4	4	16	Water: 35-40% Time: 6-8min	Multivariate experiments have demonstrated that controlling water quantity and time within these ranges significantly reduces the probability of granule densification.



Questions raised at MAA review

Prod. A, cont.

-Q3:

*“Quality risk assessment review: **severity** expresses the impact of a failure mode on quality. **Even if detectability is increased (reducing the risk priority numbers), this does not allow reducing the individual severity scores.** Risk priority numbers are also reduced invoking better failure mode detectability thanks to discriminatory dissolution and uniformity tests. However, these tests are not performed in routine. **Risk review approach should be reconsidered.**”*

-Q3 Background:

(see next slide)

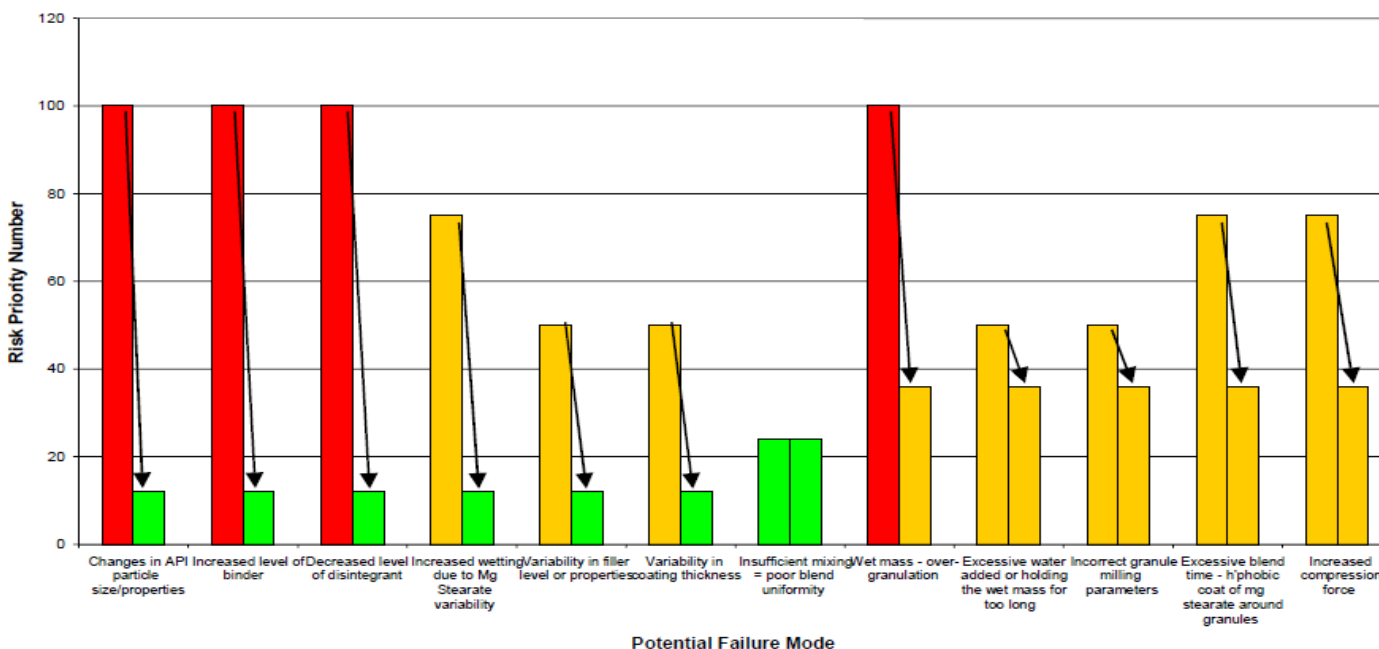


Response to Questions raised at MAA review

Prod. A, cont.

Fig: *In vivo* performance QRA 2 – product 1

RPN impacting in vivo performance after definition of the formulation elements of the DS_p & the associated control strategy



Key to risk assessment:

- = High risk of failure mode impacting in vivo product performance^a (^a = Risk was assessed considering probability, detectability and severity)
- = Medium risk of failure mode impacting in vivo product performance^a
- = Low risk of failure mode impacting in vivo product performance^a



Response to Questions raised at MAA review

Prod. A, cont.

High RPN values (**red**): *changes particle size, increased level binder, decreased level disintegrant, wet mass over granulation.*

-Q3 Response: (Summarised for presentation, full version in appendix)

QRA 1 performed prior to pivotal clinical study, to prioritise further work.

Severity scored highest due to lack of knowledge of impact .

Tablets with broad range failure modes were then tested in vivo.

Dissolution performance had lower impact on in-vivo performance

Severity scores reduced.

Risk prioritisation remained the same, but overall risk level reduced

-Q3 Assessment:

Acceptable; sufficiently justified.



Regulators remarks on applicants documentation of risk assessment

- It is positive to remark, that the applicants use suitable procedures like risk analysis and design of experiments to evaluate the potential risks. The tool most often used is the FMEA and the *results are nowadays in general comprehensively documented.*
- Other techniques to additionally **summarize all potential parameters** in a nutshell like fishbone diagrams are only sometimes used; they are encouraged.
- *It is noted that* in some cases the goal of the risk management was not to minimize the risk for the patient but for economic reasons: this would normally not be included in the regulators' assessment.



ICH Quality IWG *Points to Consider* regarding ICH Q8/Q9/Q10

Basic policy for Risk Assessment

Relationship between risk and criticality:

Risk includes severity of harm, probability of occurrence, and detectability, and therefore the level of risk can change as a result of risk management.

Quality Attribute criticality is primarily based upon severity of harm and does not change as a result of risk management.

Process Parameter criticality is linked to the parameter's effect on any critical quality attribute. It is based on the probability of occurrence and detectability and therefore can change as a result of risk management.



Regulators Review of Risk Assessment

- Risk assessment should be carried out **initially** and be **repeated throughout development** in order to assess in how far the identified risks have become controllable. The time point of the risk assessment should be clearly stated.
- A summary of all **material quality attributes** and **process parameters** which may have an impact on product quality should be presented.
- Often, only a summary table is presented **without explaining how the risks have been classified**. This is not sufficient. The risk assessment **tool** (e.g., FMEA) should be stated and **scoring** and **thresholds** used to classify the risks should be explained.
- It should be checked whether **all known risk factors have been included** (e.g., degradation).



Regulators Expectations for Presentation of Risk Assessment *cont.*

- Risk ranking outcomes not in line with the existing scientific knowledge should be justified.
- The link between risk assessment and drug substance / drug product specification should be clear. The **absence of potential CQA in the specification should be justified.**
- It should be checked **whether the identified risks are managed by the Design Space or the proposed control strategy.**
- Information on the Applicant's experts carrying out the risk assessment is not required.
- Good **example** for a risk assessment table is presented in the training material of the **ICH Q-IWG** on the implementation of Q8/Q9/Q10. Scoring and thresholds used to classify the risks are provided and risks discussed in the comments column. (Appendix)



Regulators General Remarks Critical (Process) Parameters

- There is often some uncertainty about the terms used in this context.
- From a regulatory point of view any parameter which might have an impact on the patient`s health is considered critical.
- Even if a critical parameter is adequately controlled, it will still be a critical parameter! (**risk <, but criticality is the same**) — *See ICH IWG points to consider slide*



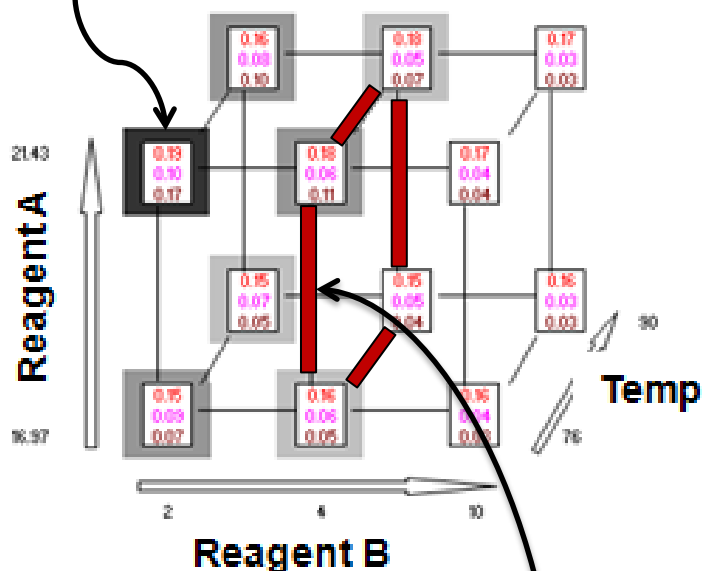
Regulators Evaluation of criticality of process parameters

- A **complete list of process parameters** plus assessment of their **criticality** should be submitted.
- No terms like “**key**”, “**major**” or “**minor**” should be used, only ICH terms.
- The **criticality assessment** of (all) the process parameters during the **development** process should be described.
- The **on-going process of risk assessment during development** should be **monitored**, i.e. risk mitigation and/or a parameter classified “non-critical” on first sight may become critical due to unexpected results during scale up
- **Critical parameters** may have significant influence on critical quality attributes of the drug product.
- **Non critical parameters** do not have significant influence on critical quality attributes of the drug product.



Industry Example for Criticality Analysis

Close to edge of failure



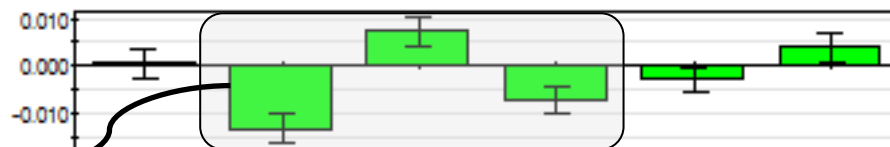
"Critical" lower limit for Reagent B

- 3 factors have statistical significance on levels of impurity B
- The factor effects are small (0.01%)
- Does not impact CQA over a wide range input parameters (2-10 mol eq)
- Defined major factor effect Reagent B as Critical (Named "Design Space Boundary") and imposed lower control limit
- All other parameters defined as Non-Critical

Discussion Point

- Parameters can have effect on CQAs and not be considered Critical

Scaled & Centered Coefficients for Imp B



Process Parameter Assessment



Learning/Best practices Risk Assessment

Companies / Regulators

- Comprehensiveness and plausibility
- Quantitative results and thresholds (if Qualitative results: thorough justification)
- Comparison to similar products evaluated before: could be useful
- Acceptance of prior knowledge of the applicant
- Assessors should not do their own risk assessment
- Asking lots of questions about details on raw data collected during development is not necessary for the marketing authorisation procedure.



Topic 2: Lifecycle Management

CHALLENGES OF USING A DESIGN SPACE



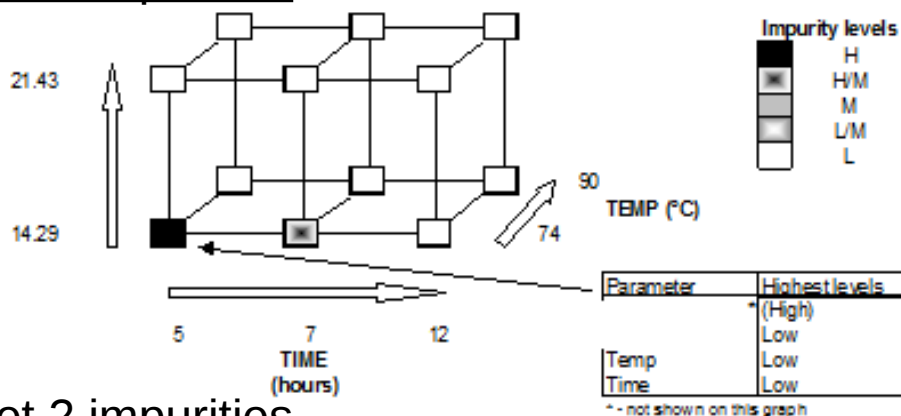
Changes when using an enhanced approach

- A MAHs Quality Management System & change management principles must be suitable for traditional and enhanced approaches
- Products with registered design spaces offer challenges to understand:
 - how they are operated at a site in practical terms using traditional documents (MBRs etc)
 - how they are managed from a compliance perspective (change & deviation management etc)
 - how risk assessment principles are embedded into the lifecycle management continuous improvement process

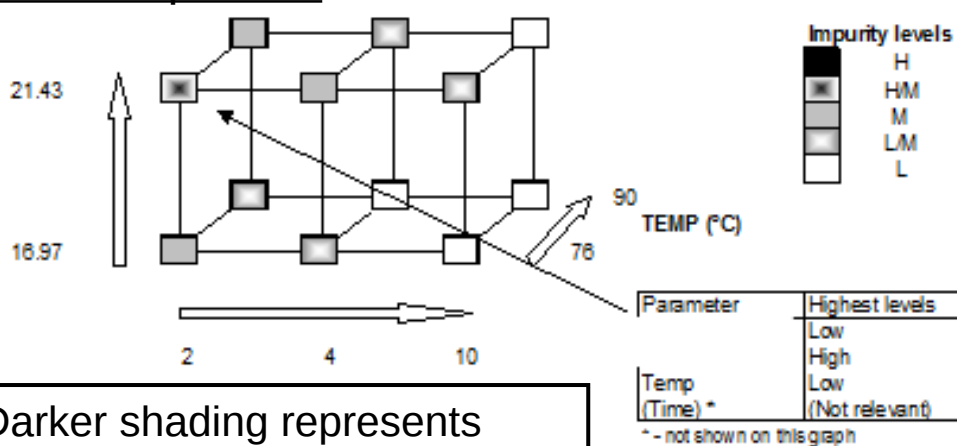


Example 1 – Escalation of Variation Category by Design Space

Set 1 impurities



Set 2 impurities



Darker shading represents higher level of criticality across the reaction space explored

Regulators Perspective

- Design Space changes are classified as Type II Variations because they should only concern critical quality parameters

Company Reflections

- A Design Space needs to have limits (2 sided ranges)
 - But there can be different degrees of criticality across a DSp
 - E.g. Extending time has no impact on API quality
- Leads to Non-Critical parameters being included in the DSp**
 - Escalation of Variation category**
- AZ would not register a DSp in these circumstances
 - Appropriate criticality could then be assigned
 - Appropriate Variation category can be ascribed (based on assessment)

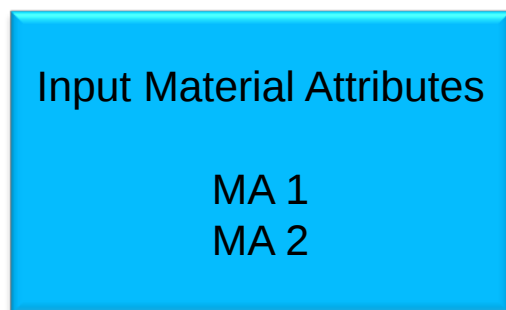


Where AZ currently see Design Space adds value

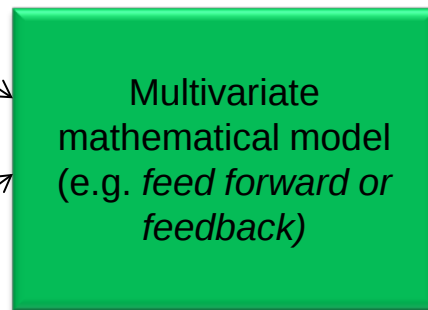
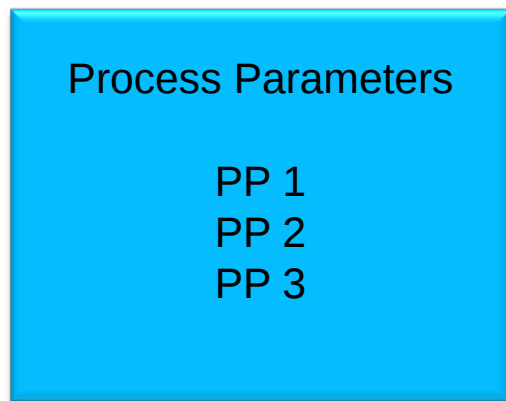
Multivariate Understanding and control of
Material Attributes &
Process Parameters during Manufacturing



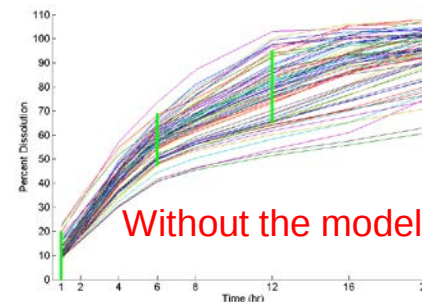
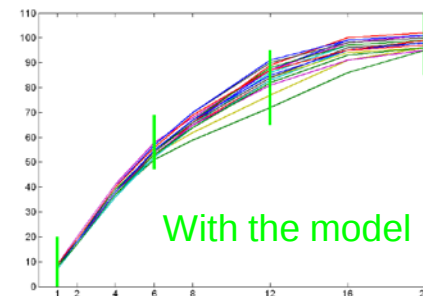
Outputs meet
the CQAs



Adaptive processes



Dissolution
Performance





Example 2 – Assessment of New information (A real situation)

- Deviation from temperature set point in commercial manufacture
 - Caused failure in API spec ‘unspecified impurities’ for one batch
 - Previously defined as ‘non-critical’ and not included in S.2.2 in the MAA
- How to interpret this change post-approval?
 - Defined as potentially critical based upon deviation investigation
- How (category or mechanism) to file new information not previously disclosed within a holistic design space?
 - Defining an ‘as is’ and ‘to be’ on a change proposal at a manufacturing site or CMO is difficult when there is no existing registered detail
- As a design space was approved was this:
 - Change within design space? No variation required?
 - A restriction to the design space? Type IA?
 - An expansion to the design space? Type II?



Example 2, cont

- A design space was registered and the new information could be perceived to affect this, but was this a Type II variation?
 - Did not seem appropriate based on results of deviation investigation
 - Potential delay to implementation
- Eventually filed as a Type IB (unforeseen)
 - EMA data requests successfully addressed and variation approved
- Design space confused decision-making on the filing strategy

Points for discussion

- Should we continue to make product by a less robust process whilst waiting for global approval?
 - QbD was supposed to enable process improvements?
- How can these types of changes be implemented quickly through a robust Quality Management System?
 - Implement in parallel with variation approval?



Outcomes & Recommendations

Example 2 - Agency Feedback

- All changes in parameters (irrespective of criticality) should be part of the risk assessment.
- Interaction between parameters and effect of multiple changes should be assessed
 - MAHs need to update process descriptions with new or changes to existing parameters set points and justified ranges
 - This is based on criticality of parameters having changed (increased) compared to the time of the initial marketing authorisation application and this needs to be appropriately reflected in the dossier.
Assessment of criticality should be in line with the risk assessment process first presented and used during the product development
 - it is the MAHs responsibility to proactively file dossier updates via a variations process to bring the file into line with the current process knowledge, standards and principles regarding the criticality level of process parameters. The Scientific Advice process can be utilised if MAHs are unsure of the filing category.



Inspection of a manufacturer of a QbD product (Inspectors view point)

GMP inspection in relation to QbD takes place at a manufacturer, probably not at the developing laboratory or the MAH.

Collaboration between assessor and inspector is beneficial, close communication between different national authorities is required, e.g. co-inspection

GMP inspector will review

Product knowledge

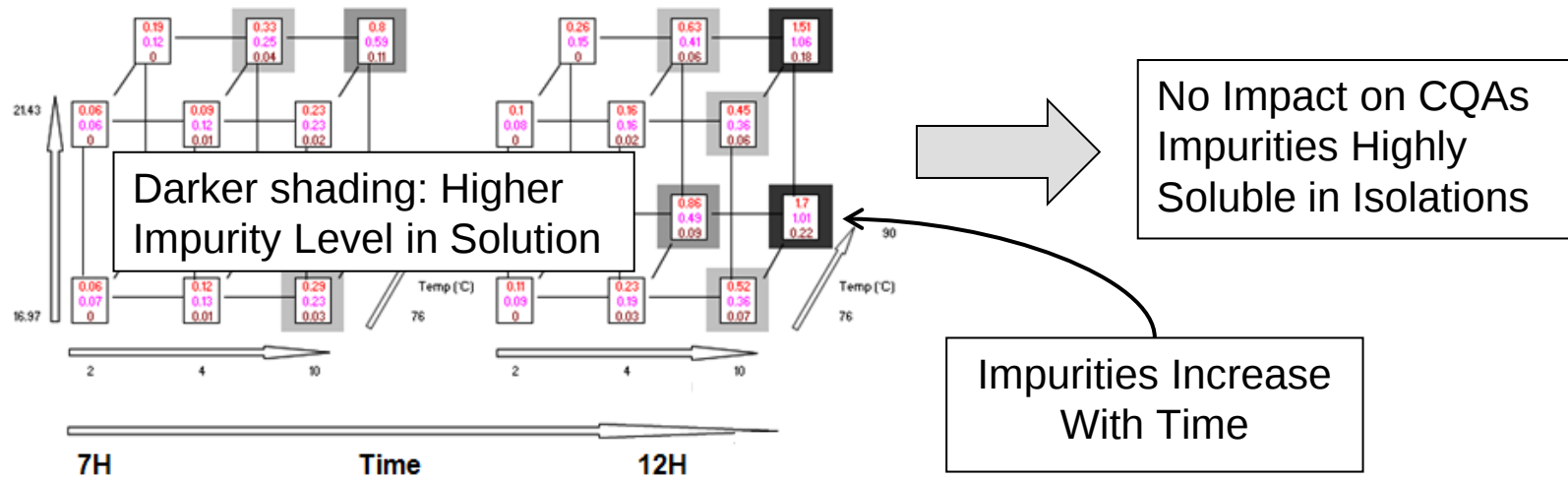
- how technology transfer between parties is ensured
- how product knowledge is managed and expanded during product maturity

Manufacturing process

- QMS supporting the life-cycle of a QbD product
- chosen control strategy to be risk assessed and correctly interpreted in process validation, both documentation and testing
- definition of deviation and handling of considered deviations during manufacturing in relation to design space and control strategy
- handling of change control



Deviation in Commercial Manufacture - Example 3



Process Understanding

- All impurities identified and relationship with reaction parameters established
- Impact of Time: Explored multivariate (12H) and univariate (24H), no impact on CQAs

MAA Proposal

- Control strategy: In-Process Test (IPT) to determine End of Reaction, “Design Space” (1 CPP)
- Proposed Time as single sided range (>5 H non-critical as IPT controls quality)

Review

- Requested to Introduce upper limit 12H (range was explored in multivariate expts)

Deviation in Manufacture

- IPT Delayed (15 H) vs range in MAA (5-12H)



How to assess Deviation using Enhanced Product Knowledge

- Could the batch be released through Quality Management System?
 - Quality: Enhanced data and rationale could justify release. **YES**
 - Regulatory: Concern due to Non compliance with MAA. **NO**
 - QP: Could be considered as a deficiency during a future site inspection
- **YES (Quality) + NO (Regulatory) = No release (AZ Assessment)**
- The range for time could be changed through a variation
 - Not a sensible approach for a one off deviation
- No perceive regulatory mechanism to permit Bx release through QMS

Points for discussion

- How can utilise enhanced knowledge & a robust Quality Management System to avoid rejecting suitable quality Bxs during production?
 - QbD should facilitate effective deviation resolution?
 - Need to establish consistency across QP/Regulatory/Manufacturing & Assessors/Inspectors



Lifecycle Management Discussion Points

- For Design Space to be of value we need to understand what it means in practice (Example 1 & 2)
 - In practice a Design Space contains both Critical & Non-Critical PP but all Variations are Type II (DSp contains a spectrum of criticality)
 - A full description of a manufacturing process is required including Critical (Design Space) and Non-Critical parameters for all products
 - But when a Design Space is approved what is the status of the “other” non-critical parameters described in the same unit operation or stage?
 - Currently causes confusion and escalates perceived risk
- Can we leverage companies QMS, inspection record and knowledge of the product to reduce change burden and manage deviations? (Example 2 & 3)
 - Agencies have data on the “Health” of a sites QMS
 - Would increase value of enhanced approach linked to cGMP & process improvement
 - Reduce delays to implementation of process improvements
- Common understanding needed between Assessors, Inspectors, Sites & QPs
 - For Global products this means cross agency harmonisation



Appendix: Additional Risk Assessment Q&A from MAA Review & supporting slides



Questions raised at MAA review

Product A *imm. release tablet - QTPP - CQAs*

D120 Questions

Module 3.2.P.2.2:

-Q 1:

“Scoring system: the gradation in the description of the severity factor should be clarified. It should be explained why severity has been related to an industrial risk rather than to an impact on product quality.”

-Q1 background :

(see next slide)



Questions raised at MAA review

Score	Probability of failure mode (P)	Severity of failure effect (S)	Detectability of failure mode/effect (D)
1	$< 1/10,000$	Deviation	Before unit operation
2	$1/10,000 - 1/1,000$	Reanalysis or minor action, then passed	During unit operation
3	$1/1,000 - 1/100$	Rejected sub batch or batch	During subsequent unit operation(s)
4	$1/100 - 1/10$	Stop in production flow for investigations	Finished product testing
5	$> 1/10$	Product recall	No means of detection



Questions raised at MAA review

Prod. A, *cont.*

-Q1 Response:

Explanation: “..wording for severity intended to represent a quality failure as this is the first point poor quality will be recognised and therefore trigger corrective action...”.

-Q1 Assessment:

Although unusual, acceptable.

-Q 2:

“In vivo performance quality risk assessment 1: *individual scores for severity, probability and detectability*, used in the calculation of risk priority numbers *should be detailed*. It should be explained *how the thresholds* to consider *low, medium or high risk* have been *defined*. It should be explained how the *probability scores* are set.”

-Q2 Response:

Details scores submitted, categorised by **formulation** & **process** variables.



Questions raised at MAA review

Prod. A, *cont.*

-Q2 Response, *cont:*

RPN calculated from the 3 scores (*probability x detectability x severity*). Individual scores 1 - 5.
Range possible RPN values: lowest: 1 – highest: 125.

Highest RPN values **formulation** variables:

Risk area	Failure mode	Failure effect	Risk analysis			
			P	S	D	RPN
Drug substance	Changes in particle size or properties, e.g. shape, surface energy, bulk properties	Changes in dissolution performance, thus impacting on clinical performance	4	5	5	100



Questions raised at MAA review

Prod. A, *cont.*

Excipients	Increasing the level of binder	Impeded tablet disintegration leading to altered clinical performance	4	5	5	100
	Decreasing the level of disintegrant	Impeded tablet disintegration leading to altered clinical performance	4	5	5	100

Highest RPN values **process** variable:

Wet granulation	Failure to control granulation end-point; Over- granulation	Decreased granule porosity, decreased water ingress and decreased dissolution rate. Adverse effect on clinical quality	4	5	5	100
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-Q2 Assessment: Accepted.



Questions raised at MAA review

Prod. A, cont.

-Q3:

*“Quality risk assessment review: **severity** expresses the impact of a failure mode on quality. **Even if detectability is increased (reducing the risk priority numbers), this does not allow reducing the individual severity scores.** Risk priority numbers are also reduced invoking better failure mode detectability thanks to discriminatory dissolution and uniformity tests. However, these tests are not performed in routine. **Risk review approach should be reconsidered.**”*

-Q3 Background:

(see next slide)

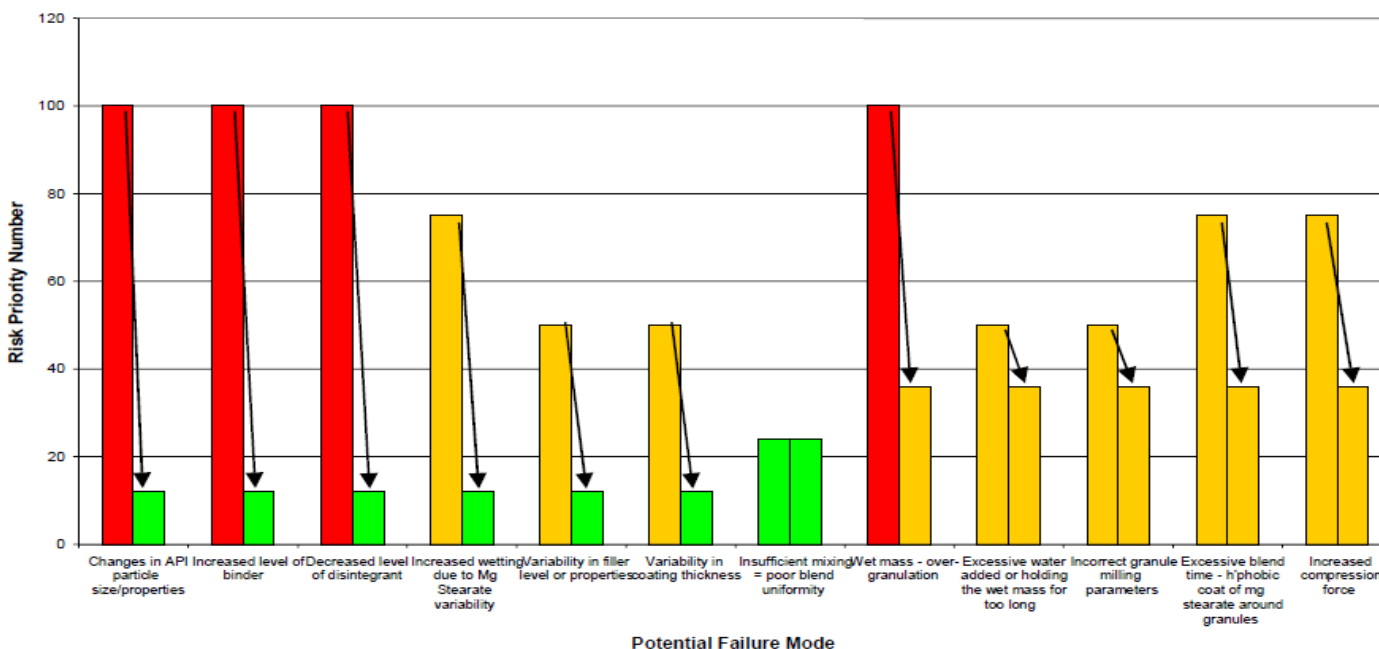


Response to Questions raised at MAA review

Prod. A, cont.

Fig: *In vivo* performance QRA 2 – product 1

RPN impacting in vivo performance after definition of the formulation elements of the DS_p & the associated control strategy



Key to risk assessment:

- = High risk of failure mode impacting in vivo product performance^a (^a = Risk was assessed considering probability, detectability and severity)
- = Medium risk of failure mode impacting in vivo product performance^a
- = Low risk of failure mode impacting in vivo product performance^a



Response to Questions raised at MAA review

Prod. A, cont.

High RPN values (**red**): *changes particle size, increased level binder, decreased level disintegrant, wet mass over granulation.*

-Q3 Response:

- Explanation: The initial in vivo performance quality risk assessment 1 was performed prior to pivotal clinical study, to prioritise further risk ranking investigation. For failure effects relating to clinical dissolution performance, severity was scored at the highest level, primarily reflecting the lack of knowledge of the extent of impact. Tablets with broad range failure modes were then tested in vivo. Following the in vivo assessment it was clear that the failure effect of clinical dissolution performance is not as severe as initially scored: **it was appropriate to reduce the severity scores**. Also plotted the risk profile for the second risk assessment if there had been no change in the individual severity scores. It is clear from this that the small adjustments made to severity do not have a significant effect on the relative classification of the risks ie, low risks remain low and medium risks remain medium.

-Q3 Assessment:

Acceptable; sufficiently justified.



Questions raised at MAA review

Product Prod. B *imm. release tablet - QTPP - CQAs*

D120 Questions

Module 3.2.S.2.2/3.2.S.2.6:

-Q 1:

".. However, in the FMECA presented, the applicant has not considered the parameter 'detectability' and has not used risks priority numbers. Qualitative descriptors as 'high', 'medium' and 'low' could be acceptable, but the applicant should show that not considering the parameter 'detectability' and the relative score numbers does not influence the Quality Risk Assessment outcome and subsequent decisions made in the development programme and quality control strategy. "

Module 3.2.P.2:

-Q 2: comparable to Q1.



Questions raised at MAA review

Prod. B, cont.

-Q 1 (Response +) Assessment:

- The applicant considers **Criticality** (Probability x Severity) a more appropriate tool for identification of risks **in development** than the RPN obtained multiplying Probability x Severity x Detectability. However, the **final QRA** includes the parameter **Detectability**.

Reasoning acceptable.

-Q 2 Response/Assessment:

Comparable to Q1.



Risk Assessment example ICH Q IWG

What is the Impact that ----- will have on purity? 1) minimal 5) moderate 9) significant						
What is the Probability that variations in ----- will occur? 1) unlikely 5) moderately likely 9) highly likely						
What is our Ability to Detect a meaningful variation in ----- at a meaningful control point? 1) certain 5) moderate 9) unlikely						
Unit Operation	Parameter	IMPACT	PROB.	Detect	RPN	Comments
Distillative Solvent Switch	Temperature / Time, etc.	1	5	1	5	Distillation performed under vacuum, at low temperature, minimizing risk of hydrolysis
Distillative Solvent Switch / Crystallization	Water content at end of Distillation (Crystallization Feed)	9	5	1	45	Higher water = higher degradation In process control assay should ensure detection and
Crystallization -- API Feed Solution	Feed Temperature	9	5	1	45	Higher temperature = higher degradation Temperature alarms should enable quick detection and control
Crystallization -- API Feed Solution	Addition Time	9	1	5	45	Longer time = higher degradation Detection of prolonged addition time may occur too late to prevent some degradation
Crystallization	Seed wt percentage	1	1	1	1	This parameters cannot impact impurity rejection, since no rejection of hydrolysis degradate occurs.
Crystallization	Antisolvent percentage (charge ratio)	1	1	1	1	This parameters cannot impact impurity rejection, since no rejection of hydrolysis degradate occurs.
Crystallization	Crystallization temperature	1	5	1	5	Temperature is low enough that no degradation will occur.
Crystallization	Other crystallization parameters	1	1	1	1	These parameters cannot impact impurity rejection, since no rejection of hydrolysis degradate occurs.