The use of in vitro and in vivo data to define both design space and control strategy.

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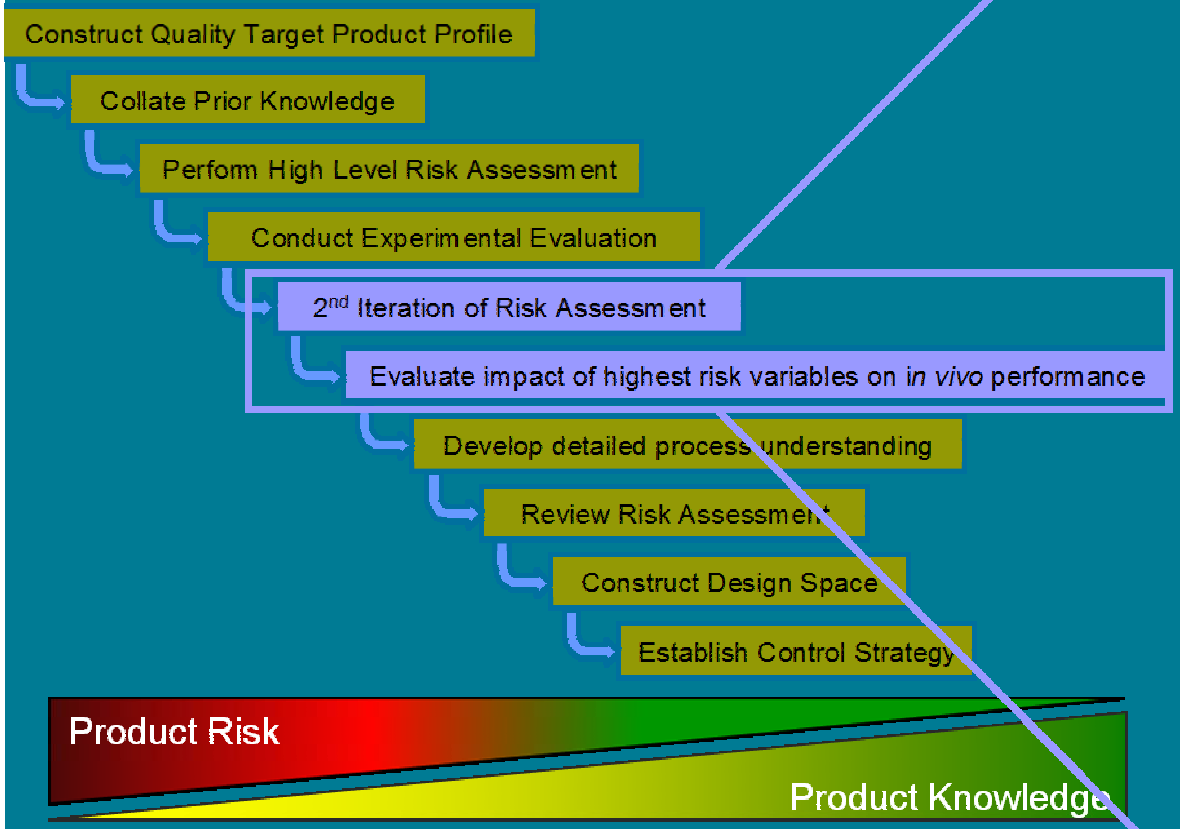
High Level Summary

- Understanding the *in vivo* impact of product and process variables is an important foundation of any QbD development
- When linked to meaningful *in vitro* tests, enables:
  - evaluation multiple aspects of the Design Space and
  - development of science and risk based specifications
- One approach, is to confirm mechanistic understanding by producing product variants that incorporate the highest risk variables and then evaluating their performance
- In this presentation we have focused on the risks relating to bioequivalence but the principles apply equally to all Critical Quality Attributes

How the AZ Case Summary Fits into the Overall QbD Development Workflow

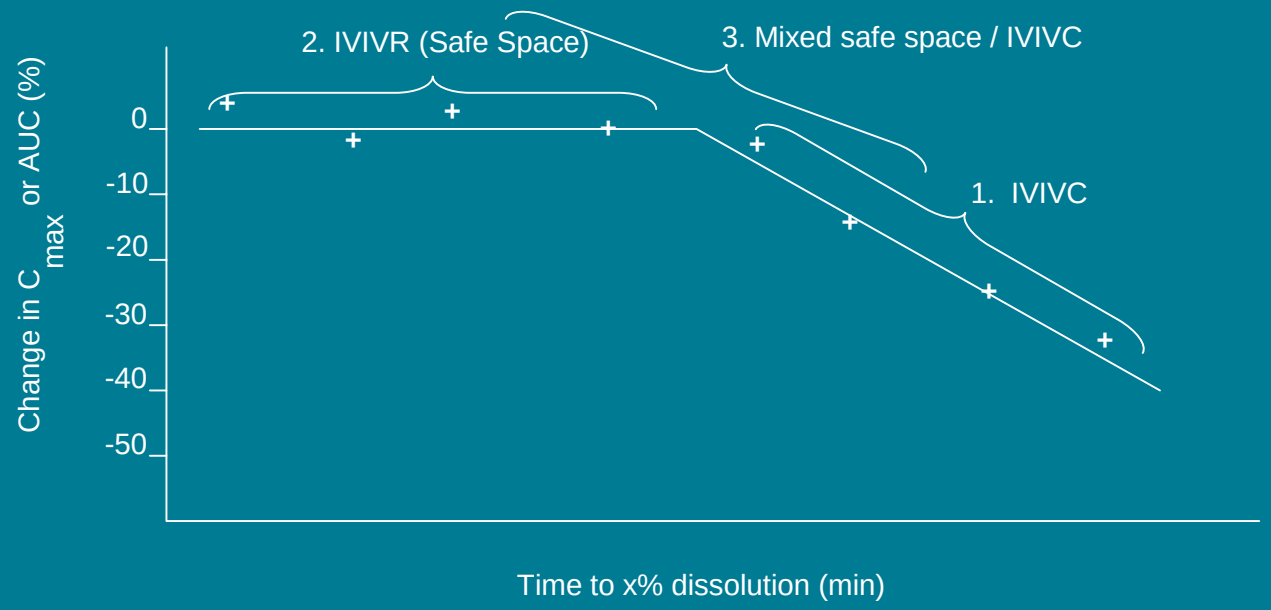
Overview of Steps in a typical QbD Development

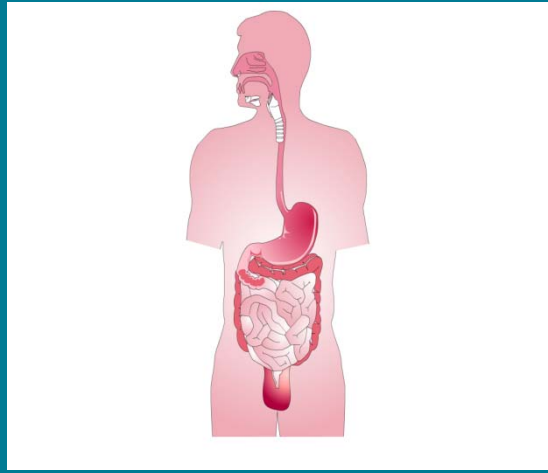


Focus of the AZ Case Studies

1. Conduct Quality Risk Assessment
2. Develop Appropriate CQA tests
3. Understand the in vivo importance of changes
4. Establish Appropriate CQA limits
5. Use the product knowledge in subsequent QbD steps

Step 3: Understanding In Vivo Impact



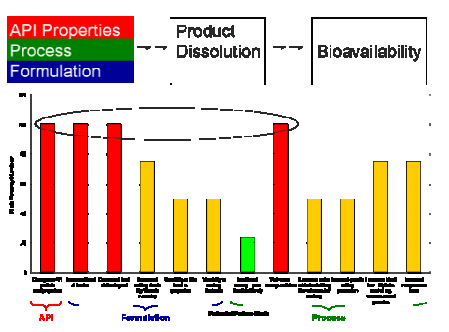


For any product three potential outcomes exist for the relationship between in vitro dissolution and bioavailability, these are:

1. A Level A or C IVIVC could be established, where changes in in vitro dissolution are directly correlated to changes in bioavailability.
2. An IVIVR in which no effect on bioavailability would be observed across a range of in vitro dissolution rates (referred as a 'Safe Space').
3. The final option is a mixed safe space / IVIVC result in which bioavailability is only affected for a few of the variants tested clinically.

Case Study 1: *In vivo* data needed – BCS2

Step 1: QRA

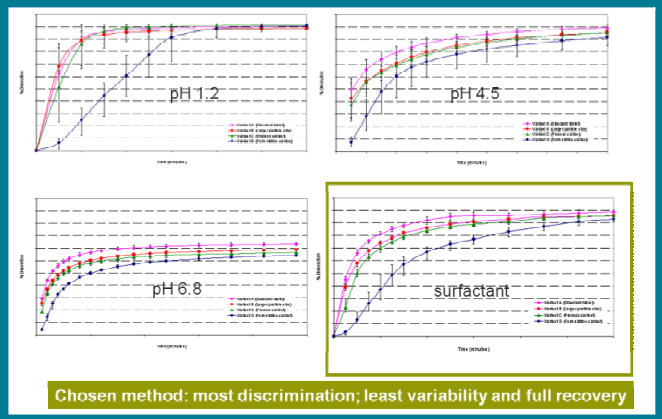


Produce Tablets variants with highest risks

Step 2: Develop CQA Test

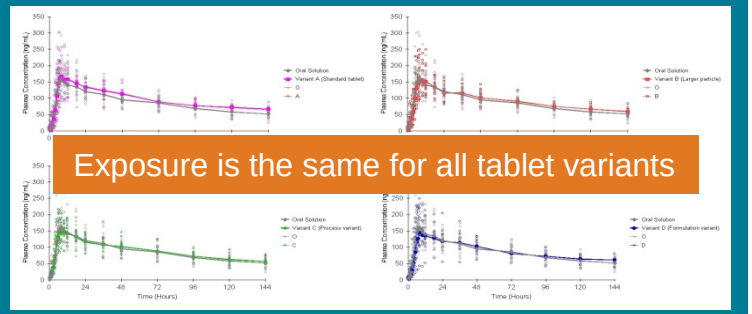
Tablet Variant	Description	Variant
A	Standard tablet	N/A
B	Drug substance particle size variant	Increased particle size
C	Processing variant	Increased water quantity and granulation time
D	Formulation variant	Increased binder and decreased disintegrant level

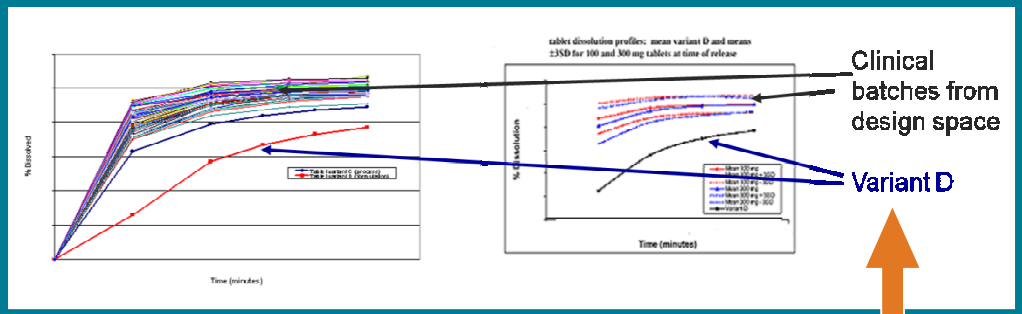
Test tablets in several dissolution conditions and find best



Step 3: Understand in vivo importance

BCS2: Need clinical data





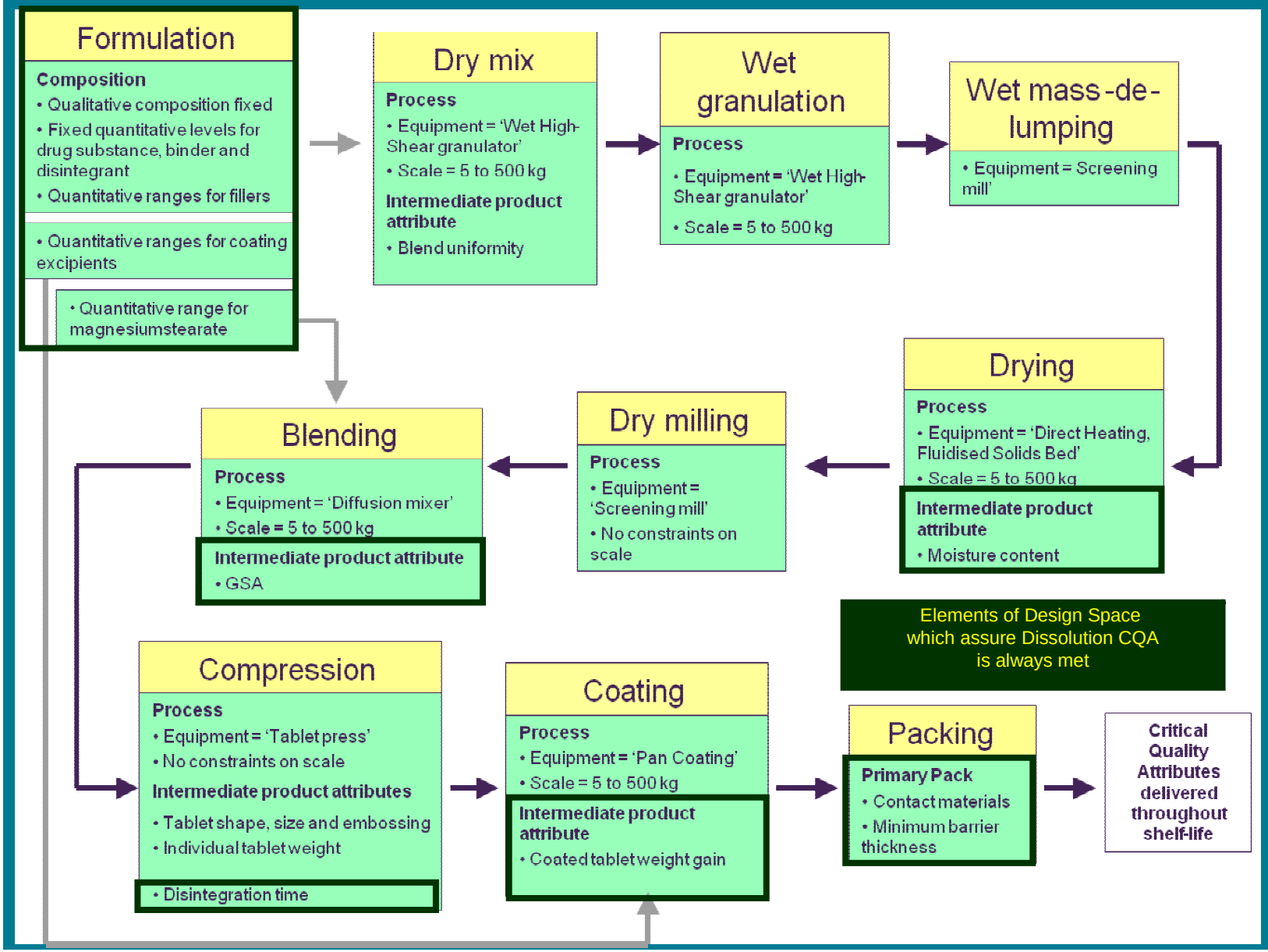
SAFE SPACE: Variant D is the limit

Step 5: Use in subsequent QbD steps

Design space boundaries defined to ensure CQA limits are always met

Step 4: Establish appropriate CQA limit

Design Space and Control Strategy



Operationally:
- scale
- process parameters
- equipment

defined in the master batch record as part of the **control strategy**

Main Topics Discussed

- Use of risk assessments & prior knowledge (e.g. BCS) to focus investigations towards understanding the impact of product and process variables on *in vivo* performance
- Setting science based specifications
- The Design Space should be developed to deliver CQAs related to Safety and Efficacy

- How to define the Design Space
- Total quality of the product
  - We need to demonstrate the ability to manufacture quality product on a routine basis
- How to operate a design space on a day to day basis
  - Change Management
  - Process monitoring throughout product lifecycle

Common Understanding

- Design space and control strategy may be linked to safety and efficacy
- Risk assessments and prior knowledge drive the development programme and may result in different approaches for different products
- BCS classification may not fully describe the biopharmaceutic risk profile of the product

- ‘Safe Space’ possible outcome for well designed BCS 2/4
  - i.e. dissolution may change to a certain extent without impacting on bioavailability
- A scientifically justified dissolution limit (possibly wider) may facilitate continual improvement of the manufacturing process against other quality attributes e.g. assay, yield, content uniformity, etc.

Areas For Further Work

- Roles of assessor and inspector
  - Content of dossier
  - What is available on site for PAI
  - How can a assessor evaluate the Change Control system relating to Design Space
- Understanding of change control / PQS (ICHQ10) / process monitoring elements in dossier
- How best to define Design Space
  - Process parameters
  - Input and Intermediate material attributes
  - Combination of both
- A dissolution specification based on in vivo data is acceptable for assurance of Safety and Efficacy but the final specification may also need to reflect the current process capability and routine quality control

Conclusion & Discussion

- Very positive interaction and exchange of ideas
- General agreement on the principles
- Main discussion focused on implementation
- Continued dialogue & the sharing of experiences is key