ICH Q8: Design Space Considerations for Dissolution Methods

Paul A Dickinson
Aim and Acknowledgements

- Review the impact of ICH Q8 on the perception and utilisation of the dissolution test

- My ideas underpinning this review have been developed in conjunction with a lot of colleagues over my professional life but especially for this talk Maria Cruañes, Talia Flanagan, Dave Holt, Arzu Selen, Sandra Suarez Sharp and Paul Stott

- Note: the views expressed in this presentation reflect my personal interpretation and the experience of individuals I have collaborated with
The context of this talk

• That the dissolution test is seen a very important quality test / critical quality attribute

• Quality by Design activities (ICH Q8) are performed to develop an understanding of the impact on dissolution and other critical quality attributes

• The design space and control strategy ensure the dissolution specification is met
The context of this talk

- That the dissolution test is seen a very important quality test / critical quality attribute
- Quality by Design activities (ICH Q8) are performed to develop an understanding of the impact on dissolution and other critical quality attributes
- The design space and control strategy ensure the dissolution specification is met

Multivariate experimentation generated granules and tablets with a wide range of properties – relationships established between process parameters, intermediate attributes and dissolution. Linear combination design space boundaries established for GSA and disintegration.

<table>
<thead>
<tr>
<th>Process Parameter</th>
<th>ANOVA (% Variance for GSA &amp; Disintegration)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dry granule milling screen size</td>
<td>48.7</td>
</tr>
<tr>
<td>Water quantity</td>
<td>16.3</td>
</tr>
<tr>
<td>Dry granule milling impeller speed</td>
<td>16.2</td>
</tr>
<tr>
<td>Wet mixing time</td>
<td>3.0</td>
</tr>
<tr>
<td>3 other factors (&lt;3.2% each)</td>
<td>8.0</td>
</tr>
<tr>
<td>Total R-squared value</td>
<td>92.2</td>
</tr>
</tbody>
</table>

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The Desired State

“A maximally efficient, agile, flexible pharmaceutical manufacturing sector that reliably produces high quality products without extensive regulatory oversight.”

Pharmaceutical Quality in the 21st Century
Janet Woodcock, M.D.
Deputy Commissioner of Operations
5th October 2005
Characteristics of the Desired State

- Systematic approach to development
- Knowledge comes from product development, prior experience, studies, scientific & technical literature
- Begins with predefined objectives
- Based on sound science and quality risk management
- Emphasizes product and process understanding and process control
  - Develop an understanding of how product attributes and process relate to product clinical performance
- Manufacturer controls the process through quality systems over product life-cycle and strives for continuous improvement
- Knowledge is shared with Health Authorities
Pharmaceutical cGMPs for the 21st Century – A Risk-Based Approach and ICHQ8

- cGMPs for the 21st century and ICH Q8 opened up of the opportunity for a lot of discussion about quality and focus fell on the dissolution test

- The design space/control strategy needs to deliver the correct dissolution performance

- Whole bunch of workshops on this matter e.g.:
FDA setting the pace?

- Biopharmaceutics reviewers move from clinical pharmacology into ONDQA
- As well as a focus on clinically relevant dissolution specifications there is movement that puts patients at the centre of drug product development

ICHQ8 R2: Quality Target Product Profile (QTPP)

“A prospective summary of the quality characteristics of a drug product that ideally will be achieved to ensure the desired quality, taking into account safety and efficacy of the drug product.”

“The quality target product profile forms the basis of design for the development of the product. Considerations for the quality target product profile could include:

- Intended use in clinical setting, route of administration, dosage form, delivery systems;
- Dosage strength(s);
- Container closure system;
- Therapeutic moiety release or delivery and attributes affecting pharmacokinetic characteristics (e.g., dissolution, aerodynamic performance) appropriate to the drug product dosage form being developed;
- Drug product quality criteria (e.g., sterility, purity, stability and drug release) appropriate for the intended marketed product.
Clinically relevant specifications

- FDA have presented on this matter extensively
- No one or two slides that capture these presentations fully:
  - “it’s not as simple as it looks” Rik Lostritto
- However there is an apparent enthusiasm to have the design space / control strategy linked to clinical performance especially through dissolution testing
- It seems FDA will actively consider clinical relevance when setting dissolution specifications
- The width of the design space / control strategy and associated regulatory flexibility are likely to be dependent on the strength of the link between the dissolution test and clinical performance of the product
Clinically relevant specifications

- Similar multi-step processes to develop clinically relevant specification for IR tablets have been proposed.
- For controlled release products, the Level A IVIVC route seems well accepted.

### Steps

<table>
<thead>
<tr>
<th>Step</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Conduct Quality Risk Assessment (QRA)</td>
<td>QRA to allow the most relevant risks (product and process variables) to in vivo dissolution to be identified (ICH Q9)</td>
</tr>
<tr>
<td>2. Develop appropriate CQA tests</td>
<td>Develop in vitro dissolution test(s) with physiological relevance that is most likely to identify changes in the relevant mechanisms for altering in vivo dissolution (identified in Step 1)</td>
</tr>
<tr>
<td>3. Understand the in vivo importance of changes</td>
<td>Determine the impact of the most relevant risks (from Step 1) to clinical pharmacokinetics based on in vitro dissolution data combined with: 1. prior knowledge including BCS and/or mechanistic absorption understanding 2. and/or clinical ‘bioavailability’ data</td>
</tr>
<tr>
<td>4. Establish appropriate CQA limits</td>
<td>Establish the in vitro dissolution limit that assures acceptable bioavailability.</td>
</tr>
<tr>
<td>5. Use the Product Knowledge in Subsequent QbD steps</td>
<td>Define a Design Space to deliver product CQAs e.g. ensure in vitro dissolution performance within established limits. Develop a Control Strategy to ensure routine manufacture remains within the design space e.g. that assures dissolution limits are met during routine manufacture (ICH Q10).</td>
</tr>
</tbody>
</table>


Japan: NIHS, PMDA and Pharma Industry

2008
- Sakura: *English Mock QOS P2_Final_June08*
  - Specification based on a clinical study
  - Dissolution heavily influenced by particle size
  - Algorithm for RTRT

2010
- Updated, more detail on RTRT

2015
- Sakura Bloom Tablets P2 Mock
  - Dissolution chosen to be discriminatory but not an obvious clinical relevance
  - RTRT based on intermediate product attributes (like hardness)

Europe

• Have seemed less interested in clinically relevant dissolution
  – at least in terms of setting specifications
  – seem to recognise clinical relevance has value in describing
    the product development in P2
• Have more focussed on discriminatory methods and ‘PAT’ and
  RTRT
Release Test and Specification

Challenges

- Global method and specification
- Based on ensuring BE between batches
- That allows the manufacturing process capability to be monitored (Continuous Process Verification) and corrective actions taken if trends observed
- That considers traditional ‘quality aspects’
- To understand and justify all these aspects a quite complicated dataset needs to be presented and interpreted.
- Interpretation may depend on which of above aspects is most important to whoever is looking at the data
**Release Test and Specification**

### Performance of the different dissolution methods against desired method capabilities

<table>
<thead>
<tr>
<th>Desired method capability</th>
<th>pH 1.2 aqueous buffer</th>
<th>pH 4.5 aqueous buffer</th>
<th>pH 6.8 aqueous buffer</th>
<th>Surfactant</th>
</tr>
</thead>
<tbody>
<tr>
<td>The ability to detect the impact of minor process and formulation changes (within design space)</td>
<td>Low. Only able to discriminate the extreme retardation mechanism</td>
<td>Low. Shows same rank order discrimination as surfactant, however high intra-batch variability, hence poor method capability/robustness.</td>
<td>High. Able to discriminate between tablet variants and hence all dissolution retardation mechanisms probed in clinical study.</td>
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</tr>
<tr>
<td>The ability to detect changes in performance of the product on storage (stability indicating)</td>
<td>Low. Does not discriminate stability changes</td>
<td>Not tested due to high intra-batch variability.</td>
<td>Not tested due to incomplete release in a reasonable time (and shows same rank order discrimination as surfactant).</td>
<td>High. Discriminates minor stability changes</td>
</tr>
<tr>
<td>To achieve complete dissolution within a timescale appropriate for a routine control test</td>
<td>Yes. Complete release in a reasonable time for an IR tablet</td>
<td>Yes. Complete release in a reasonable time for an IR tablet</td>
<td>No. Incomplete release in a reasonable time.</td>
<td>Yes. Complete release in a reasonable time for an IR tablet.</td>
</tr>
<tr>
<td>Practical for routine use (timescale, ease of use of media)</td>
<td>Yes. Media simple to prepare.</td>
<td>No. Small changes in media pH likely to affect dissolution performance.</td>
<td>No. Complete release not achieved within a timescale appropriate for a routine control test.</td>
<td>Yes. Media relatively simple to prepare.</td>
</tr>
<tr>
<td>The methodolgy should be able to assure in vivo performance, ie, it can be used to set a specification which assures that tablets will give equivalent clinical performance to those used in pivotal clinical studies</td>
<td>Medium/High. Over-discriminatory with respect to one in vivo failure mode. Based on the knowledge of clinical study, and dissolution in the small intestinal environment (pH 6.8, FaSSIF) a conventional IR specification can be set to assure equivalent exposures to pivotal clinical studies.</td>
<td>Low. There is high intra-batch variability, hence poor method capability/robustness; difficult to set a specification that would pass acceptable batches and fail unacceptable batches.</td>
<td>Low. Over-discriminatory with respect to all in vivo failure modes. Incomplete release means that it is difficult to set a conventional IR specification to assure equivalent exposures pivotal clinical studies.</td>
<td>Medium/High. Over-discriminatory with respect to all in vivo failure modes; specification can be set to assure equivalent exposures to pivotal clinical studies.</td>
</tr>
<tr>
<td>Physiological relevance of the media</td>
<td>Medium/High. Acidic media reflects average stomach environment and resonance time.</td>
<td>Low. At best pH 4.5 is only found at the proximal duodenum.</td>
<td>Medium. pH 6.8 reflects the small intestine, but solubility lower due to lack of bile acid mixed micelle solubilisation.</td>
<td>Medium/High. Surfactant mimics small intestinal environment including bile acid mixed micelle solubilisation, and similar drug solubility as HIF and FaSSIF.</td>
</tr>
</tbody>
</table>
Discriminatory power and complete release vs process capability

• A discriminatory dissolution method without a clinically relevant specification can reduce process capability and potentially impact security of supply.
• Setting the specification only on development data, when the full spectrum of commercial process variation has not been experienced\(^1\), can lead to failing clinically acceptable batches.
• This is an important barrier to overcome.

Discriminatory power and complete release vs process capability

- Two methods that discriminate between tablet variants that are equivalent in the clinic.
- Different level of discrimination
- If Q and time are not considered in the context of clinical relevance there is a penalty to developing a more discriminatory method
- The more discriminating method fails 4% of clinically acceptable batches (1 in 25) with Q=80
- With Q=70, would only fail 1 in 10,000 clinically acceptable batches
- The less discriminating method would only fail 3 batches per million with Q=80
f2 testing with a clinically relevant method and specification to support post-approval changes

- For products with a clinically relevant method and specification, f2 similarity testing as a surrogate for clinical similarity is rendered unnecessary/obsolete
  - product pre/post change should be assessed against the specification
- However some regulatory guidance may require f2 testing for post-approval changes not specifically covered in design space
  - API site change
- Propose to redefine the f2 pass value (from the standard 50) to a new value based on clinically relevant batches / pivotal batches
- \( f2 \approx 35 \)
- \( > \bullet = \text{clinically acceptable batch} \)
BioRAM

• A proposal to better integrate preclinical, pharmaceutical and clinical development for patient benefit
• Intimately linked to clinically relevant specifications and methods.
• J. Pharm. Sci 103: 3377–3397, 2014

**Dissolution:**
In early product development / technology selection to:
Screen Technologies
Select technologies with likely required in vivo performance
Provide early insight into key quality attributes

**Dissolution:**
Late Phase 2 and Phase 3
Moves to precise control of in vivo performance (aspirational?)
Control of product quality

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**The Biopharmaceutics Risk Assessment Roadmap for Optimizing Clinical Drug Product Performance**

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**ICH Q8: Design Space Considerations for Dissolution Methods**
BioRAM

- An holistic approach to product development might change our perception and understanding of CQAs?

Possible Approaches for Clinically Relevant specification for drug dissolution/release

Based on assuring bioequivalence to the clinical trial batch (common approach)

Hybrids and other (?) methods

QTPP-driven: Product characteristics critical for therapeutic benefit as identified in QTPP (Quality Target Product Profile) guide selection of appropriate drug product and process design and development. Careful characterization of CQA’s and critical process parameters with appropriate biopharmaceuticals studies, result in desired in vivo performance, and thereby, enable linking product, process, and patient (desired therapeutic outcomes).

Arzu Selen. Navigating the Biopharmaceutics Risk Assessment Road Map (BioRAM): Therapy-Driven QTPP Strategies for Clinically Relevant-Specification Setting Workshop.
BioRAM: an example of a more holistic approach to developing clinically relevant CQAs

- Product design and dissolution with a specific patient need in mind: product for migraine

**Scenario 1 – Rapid Therapeutic Onset**

Box 4 – Refined Formulation Studies

- Salt Screens → Amorphous & Crystalline Potassium Salts


- LFC of Potassium Salt in PEG with surfactant
- Preclinical and clinical PK studies show LFC superior to solid dosage forms of the potassium salts
- LFC (SGC) used for Phase II trials but too large plus poor stability impacts in vivo release!

**Arginine Alkalizer level:**

**Tablet Dissolution at Gastric pH**

- At pH 1, the greater the alkalizer level, the faster the dissolution
- At pH 2, impact of alkalizer level is less pronounced

*USP II, 100 rpm, media contains Tween 80 surfactant solubilizer.

Maria Cruañes. Navigating the Biopharmaceutics Risk Assessment Road Map (BioRAM): Therapy-Driven QTPP Strategies for Clinically Relevant-Specification Setting Workshop.
Real Time Release Testing: “wot no dissolution”

- Real Time Release Testing (RTRT) is the ability to evaluate and ensure the quality of in-process and/or final product based on process data
  - Typically include a valid combination of measured material attributes and process controls
- It seems that FDA enthusiasm is catching up with other agencies

Christine Moore courtesy of Sandra Suarez Sharp:
Conclusions

• Although the dissolution test look technically simple it can bridge from clinical to formulation to process to RTRT
• So it is a key CQA that the design space / control strategy needs to assure
• The move to clinically relevant specifications is an opportunity to have better products. But if specification thinking is mixed with traditional quality specifications there is a potential, unneeded, threat to product supply
  – And the advantages of discriminatory methods will be lost
• Structured approaches to (clinically relevant) dissolution methods and specifications development are being published. These may ensure that factors relevant for performance are identified, their impact understood and a test with the necessary sensitivity identified
  – Microscopic: the 5 step process
  – Macroscopic: BioRAM
• Dissolution is complex and so need to involve experts from many areas with a ‘systems mindset’ to really leverage the value of this ‘simple’ tests and efficiently develop products with optimal quality
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