Dissolution and clinically relevant specifications: linking clinical performance to dissolution

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Key messages

• A structured 5-step approach to developing clinically relevant dissolution methods and specifications will be presented, which ensures that risks to clinical performance are identified and their impact understood.

• Benefits include:
  • the ability to optimize the manufacturing process and evaluate changes based on \textit{in vivo} performance,
  • enhanced security of product supply,
  • improved assurance of the clinical quality of product supplied to patients.

• However, the demands of discriminatory power and demonstration of complete release can sometimes be at conflict – this is an important barrier to overcome.

• Further work in our scientific understanding and regulatory harmonization are needed to realize the full benefits of clinically relevant specifications.
Approaches to link dissolution to clinical quality
Overview of Steps in a typical QbD Development:

1. **Collate Prior Knowledge**
2. **Perform High Level Risk Assessment**
3. **Conduct Experimental Evaluation**
4. **2nd Iteration of Risk Assessment**
   - Evaluate impact of highest risk variables on *in vivo* performance
5. **Develop detailed process understanding**
6. **Review Risk Assessment**
7. **Construct Design Space**
8. **Establish Control Strategy**

Focus of 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**

**Development of *in vivo* understanding:**

- Construct Quality Target Product Profile
- Collate Prior Knowledge
- Perform High Level Risk Assessment
- Conduct Experimental Evaluation
- 2nd Iteration of Risk Assessment
  - Evaluate impact of highest risk variables on *in vivo* performance
- Develop detailed process understanding
- Review Risk Assessment
- Construct Design Space
- Establish Control Strategy
Structured five-step approach to build *in vivo* understanding: Dissolution CQA

<table>
<thead>
<tr>
<th>Step</th>
<th>Example</th>
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</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>
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<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:</td>
</tr>
<tr>
<td></td>
<td>1. prior knowledge including BCS and/or mechanistic absorption understanding</td>
</tr>
<tr>
<td></td>
<td>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 Control Strategy to deliver product CQAs i.e. that assures dissolution limits are met during routine manufacture (ICH Q10).</td>
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Dissolution – Mechanistic Understanding

Note: there are more underlying product and process attributes that might influence dissolution rate than listed above!
Is an *in vivo* study always required?

- For BCS 1 and 3 compounds, the ‘Safe Space’ across which bioequivalence is assured, is already well defined.

<table>
<thead>
<tr>
<th>Solubility</th>
<th>Permeability</th>
<th>Bioequivalence Study</th>
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</thead>
<tbody>
<tr>
<td>High</td>
<td>1</td>
<td>High: Complete dissolution within 30 minutes in most discriminating ‘simple’ media (physiological pH range). If slower: bioavailability data or additional mechanistic information</td>
</tr>
<tr>
<td>Low</td>
<td>2</td>
<td>Low: Limit set on case by case basis: Bioequivalence Study Or Follow principles of BCS2 or BCS3 if can demonstrate that compound behaves more like BCS2 or BCS3 in vivo</td>
</tr>
<tr>
<td>High</td>
<td>3</td>
<td>High: Complete dissolution within 15 minutes in most discriminating ‘simple’ media (physiological pH range). If slower: bioavailability data or additional mechanistic information</td>
</tr>
<tr>
<td>Low</td>
<td>4</td>
<td>Low: Limit set based on clinical ‘bioavailability’ data</td>
</tr>
</tbody>
</table>

Further *in vitro/in silico* approaches

- Other approaches besides the generation of clinical data are available to study the potential *in vivo* impact of process and formulation variables, eg:
  - Biorelevant media and apparatus (simple, complex)
  - Preclinical models
  - *In silico* absorption modelling
- Some or all of these approaches will always have a place in building product understanding
- There will be a heavier emphasis on these methods for compounds where healthy volunteer studies not possible (eg. some cytotoxics)
Possible relationships between dissolution and drug bioavailability

* Assuming in vitro dissolution mechanistically similar to in vivo dissolution. A 4th outcome is differences in vivo that are not replicated in vitro.
Produce tablet variants with highest risks

Test tablets in several dissolution conditions and find best

Step 1: QRA

Step 2: Develop CQA Test

Step 3: Understand the in vivo importance of changes

Step 4: Establish appropriate CQA limit

Step 5: Use in subsequent QbD steps

- Control Strategy defined to ensure CQA limits are always met
- Control Strategy boundaries confirmed (Tablets variant X)

SAFE SPACE: Variant D is the limit

Exposure is the same for all tablet

BCS2: Need clinical data

Case Study 1: BCS2, *in vivo* data needed
Case Study 2: BCS3/4, *in vitro* only approach

**Step 1: QRA**
- Process, formulation and API risks identified
- ‘BCS3-like’ *in vivo* risk profile:
  - Rapid dissolution in aqueous buffers and FaSSIF,
  - High DIDR\(^1\) across phys pH range,
  - Tablet = solution,
  - Linear PK

**Step 2: Develop dissolution tests**
- Used aqueous buffers across the physiological pH range (pH 1.2, 4.5 and 6.8)
- FaSSIF also used to understand lubrication risk (Mg stearate interaction at pH 6.8 led to incomplete release)

**Step 3: Understand *in vivo* importance**
- Level of risk similar to BCS 3 so used >85% in 15 minutes as acceptance criterion

**Step 4: Establish appropriate CQA limit**
- *In vitro* data plus BCS 3 ‘prior knowledge’ gave sufficient assurance of no *in vivo* impact if acceptance criterion was met – no need to gather further clinical data to support control strategy establishment

**Step 5: Use in subsequent QbD steps**
- Control strategy defined to ensure BCS 3-like performance maintained during routine manufacture (Q=80 in 15 minutes)
- Manufacturing process explored, can’t slow dissolution even beyond meaningful process ranges – driven by high solubility of API
- One of the simple aqueous media was selected for use as a routine QC media
  - need complete release for QC use

\(^1\)Yu et al. 2004 Int J Pharm 270:221-7
How have clinically relevant methods and specifications worked in practise?
Some challenges we’ve encountered…
Dissolution - What are the aspects we are trying to balance?

Under-Discrimination
(Patient Risk)

- Poor Quality batches released – impact on safety & efficacy
- Fail to measure important failure mechanisms

Over-Discrimination
(Producer Risk)

- Fail clinically acceptable batches
- Impact Manufacturing Process Capability (introduce variation)

Challenges

- Global method and specification
- Based on ensuring BE between batches
- That allows the manufacturing process capability to be monitored (Continued 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
Absence of harmonised approach between regulatory authorities

• The desirable scenario from a commercial supply perspective is to have a **single global supply chain**.

• In practise, discussion of clinically relevant methods and specifications during the NDA/MAA process can lead to **different outcomes in different territories**.

• For AZ, this has lead to the same product having different specifications and sometimes even dissolution methods approved in different territories.

• This complicates release testing during commercial manufacture and the subsequent supply chain.

• This was the subject of a roundtable discussion at AAPS 2013*
Absence of harmonised approach between regulatory authorities: Case Study 1

pH 1.2

pH 4.5

pH 6.8

surfactant
Balancing discrimination vs complete release

Tighter specification = better quality?

• For some pharmacopoeial tests, the acceptance limits are absolute measures;
  • e.g. assay limits of 90-110% guarantee that the product contains between 90 and 110% of the label claim

• However, this is not true of Q=80% for dissolution - the meaning of ‘Q=80’ is dependant on the discriminatory nature of the dissolution method
  • Driven by solubility of drug (and excipients) in the test media

• Have to balance the need to discriminate failure mechanisms vs. extent of release
Balancing discrimination vs complete release

Discriminatory power 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 vs \(Q=80\)

Impact in routine commercial manufacture

- 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 \(Q=80\) – potentially this provides a less stringent assessment of quality.
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Thank you for your attention!