Clinically Relevant Specifications in Practice: What Have We Learned Since the QbD Pilot Program?

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Aim and Acknowledgements

- Review the journey we have gone on since the early 2000s
  - What has been good
  - Where we might go in the future
  - What challenges remain
- Focussed on oral immediate release products

- 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, Jack Cook, Filippos Kesisoglou and Paul Stott

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

Dissolution

- On the outside crude test with an uninspiring, bad 1970's design
  - USP 1970: "1 liter beaker with a slightly concave bottom"
- However the applied science that it can capture makes it one of the most talked about, important and emotive tests
  - Quality
  - Clinical performance

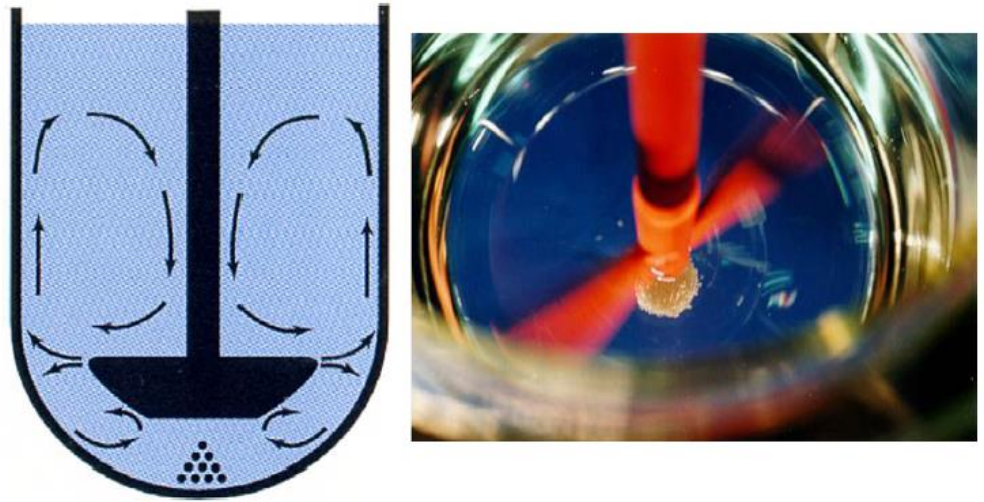
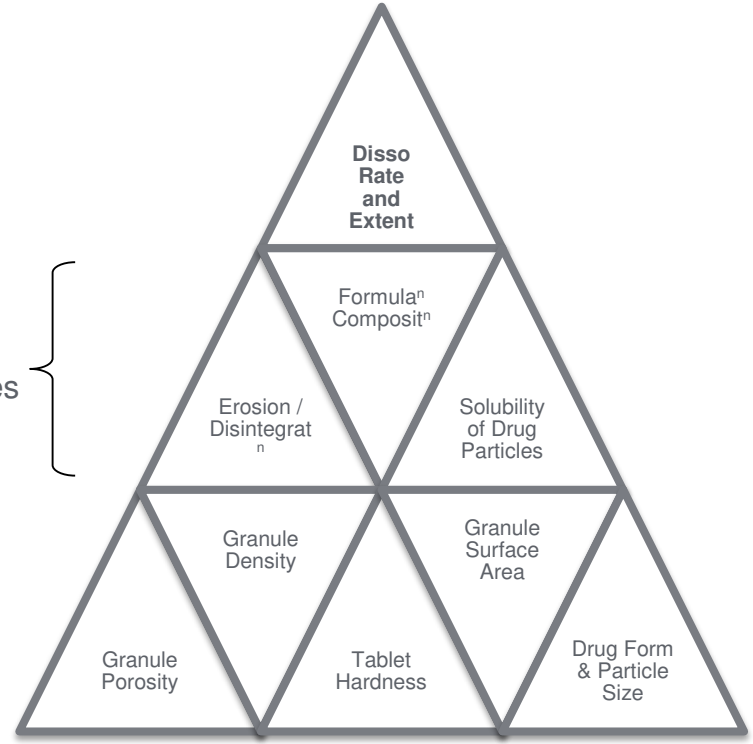


Fig. 2. Coning below paddle in the USP 2 apparatus.

Quality Aspects:
Mechanistic understanding and dissolution

Test to ensure
Manufacturing
Consistency / QC method

More specific testing & control



Product attributes

Process linked product attributes

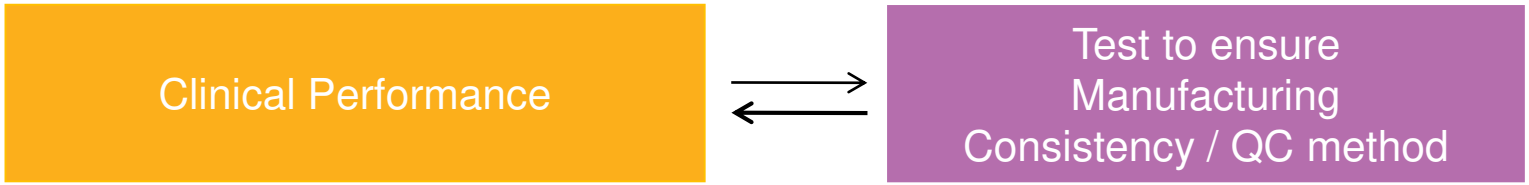
More general testing & control

Test to ensure
Clinical Performance:

Dissolution is the first step in drug absorption and therefore may affect Patients Pharmacokinetics

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



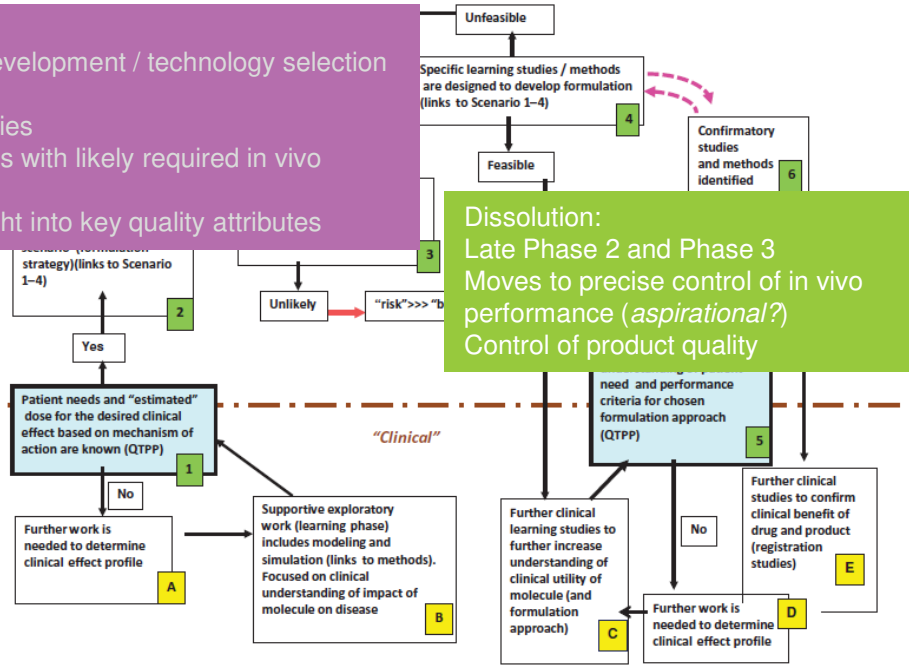
- **The design space/control strategy needs to deliver the correct dissolution performance**
- Whole bunch of workshops on this matter.
- FDA setting the pace?
  - Office of New Drug Quality Assessment (ONDQA) in late 2005 (2015: Office of New Drug Products (ONDP)
  - Biopharmaceutics reviewers move from clinical pharmacology into ONDQA

The Future?: BioRAM

- A proposal to better integrate pr
  pharmaceutical and **clinical d**
  for patient benefit
- Intimately linked to clinically rele
  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



The Biopharmaceutics Risk Assessment Roadmap for Optimizing Clinical Drug Product Performance

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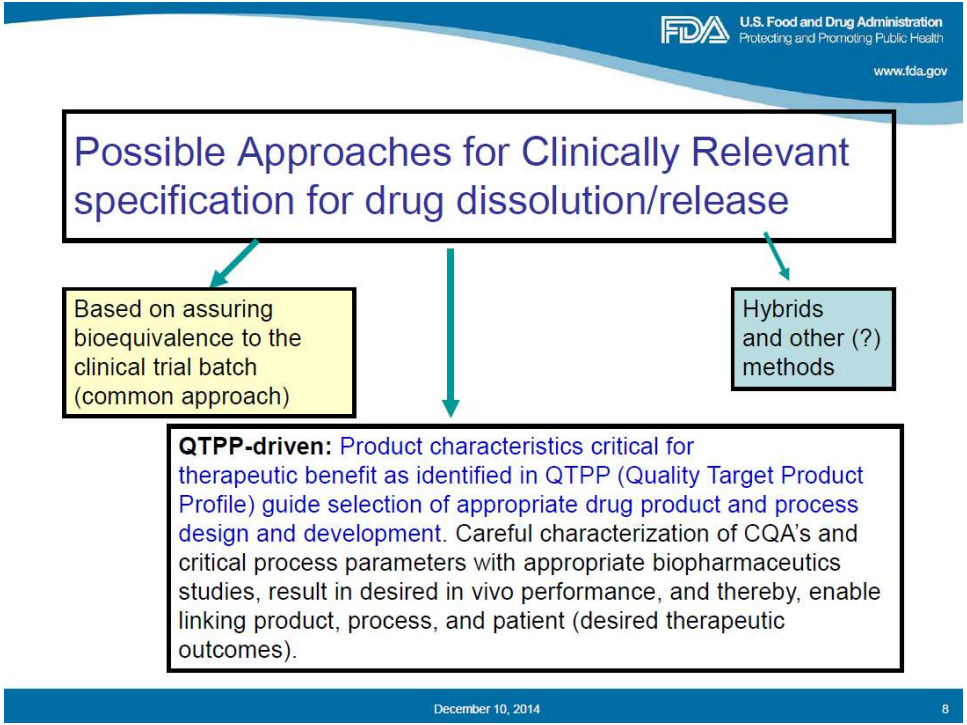
Figure 4. The Biopharmaceutics Risk Assessment Roadmap (BioRAM).

The Future? BioRAM

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



Arzu Selen. Navigating the Biopharmaceutics Risk Assessment Road Map (BioRAM): Therapy-Driven QTPP Strategies for Clinically Relevant-Specification Setting Workshop.

My personal view of this drive towards patient benefit

- It is a very good thing
- Increased probability of developing products that:
  - Optimally meet the patient's needs
  - Increases the probability of successful development
  - When combined with ICH Q8 / QbD thinking results in a robust supply chain

The Remaining / Ongoing Challenges

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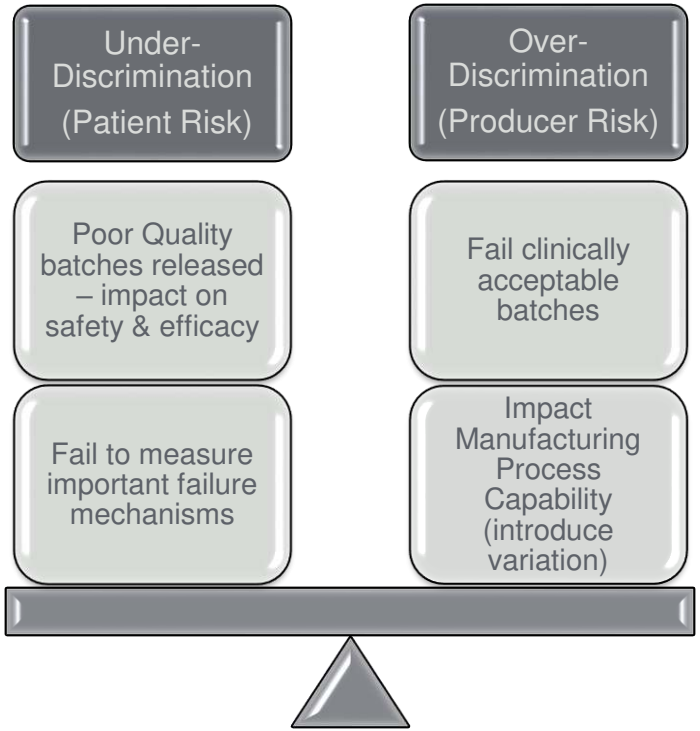
Clinically relevant specifications and ICH regions

- An industrialists (my) perception:
  - FDA positive and leading the thinking in this area and actively consider for the release test and specification
  - EMA are more focused on discrimination and traditional quality attributes / pivotal batch history
  - NIHS/PMDA seemed positive but it is missing in their latest Mock P2

- This has an serious impact on companies working globally……

Choice of Release Test and Specification

Recent news: FDA Draft Guidance: Dissolution Testing and Specification Criteria for Immediate-Release Solid Oral Dosage Forms Containing Biopharmaceutics Classification System Class 1 and 3 Drugs



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

Choice of release test and specification

- It is quite a difficult decision anyway and the Industry is probably feeling a bit confused as the different Agencies seem to have somewhat mutually exclusive demands for the test:
  - Choice of media
    - Biorelevant media (gastric pH)
    - Discriminatory media
    - Appropriately discriminatory media
  - Specification based on batch history vs clinical relevance
  - Dissolution media volume

Discriminatory tests: specification setting and F2 testing

- A discriminatory test would seem desirable:
  - Increased detectability (ICH Q9)
  - Increased understanding
  - Facilitate CPV
- However if the specification is set without consideration of clinical relevance there is a penalty (increased probability failing clinically acceptable batches) to developing a discriminatory method
- F2 testing should be obsolete if a clinically relevant specification exists and the batches for comparison meet the specification
  - If there are legal requirement to do F2 testing then the pass value (usually set to 50) should be redefined based on the range of clinically acceptable batches

Developments required in the use of clinical studies to inform on clinically relevant specifications

- More thinking required on the side batches / variants to be dosed in Healthy Volunteer studies
  - Univariate vs multivariate side batches?
  - Does it have to be all failure modes or just the high risk ones?
  - Does the likely outcome (Safe space vs IVIVC) affect the choice?
  - Need to meet BE limits?
  - For IR
    - Safe space
    - Should a rank order / level C be good enough if we can define a cut off point
      - Fundamentally different to MR
  - Underpinned with in vitro and in silico data?

Developments required in the use of clinical studies to inform on clinically relevant specifications

  - How can we leverage data across studies
    - Pop PK
    - Rel BA vs Solution?
    - Abs BA?

- Patient only Drugs (e.g. Oncology)
  - Unlikely that can dose to HV
  - Open to altered metrics, correct for carry over etc
  - More reliance on cross study comparison (Pop PK etc)

Conclusions

- We need to ask “What is most important aspect of product quality that the the dissolution test is providing information on?”
  - What can we do to align thinking across ICH regions on this matter
- If we do this will is result in consistent demands for the dissolution test?
- Can we agree on the lack of relevance for F2 testing if there is a clinically relevant specification?

- Is the physical design of the test fit for the 21st Century?

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