Pharmaceutical Development Services

ICH Q8: Design Space Considerations for Dissolution Methods

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JPAG JOINT PHARMACEUTICAL ANALYSIS GROUP

Impact of emerging regulatory guidelines on development and commercial activities
Monday 7th September 2015

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**

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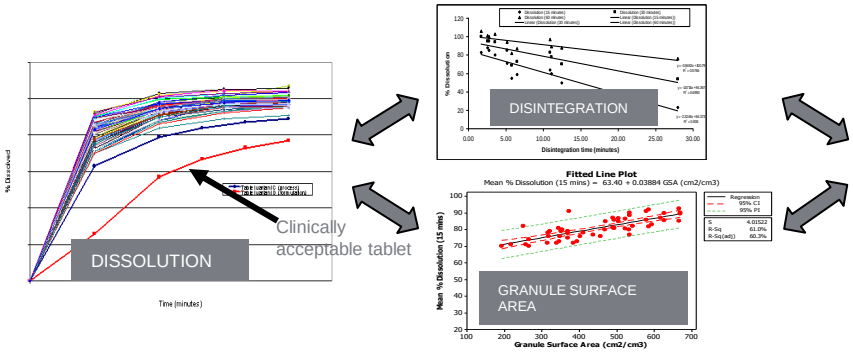
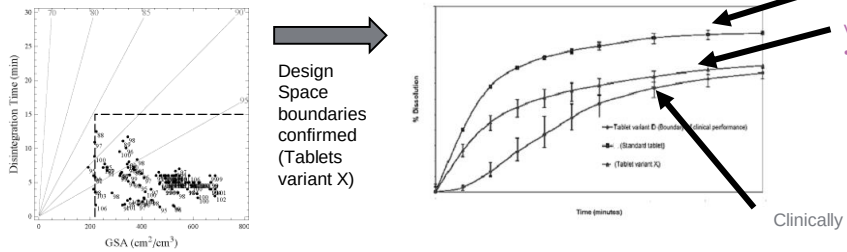


Process Parameter	ANOVA (% Variance for GSA & Disintegration)
Dry granule milling screen size	48.7
Water quantity	16.3
Dry granule milling impeller speed	16.2
Wet mixing time	3.0
3 other factors (<3.2% each)	8.0
Total R-squared value	92.2

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.



The Desired State

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

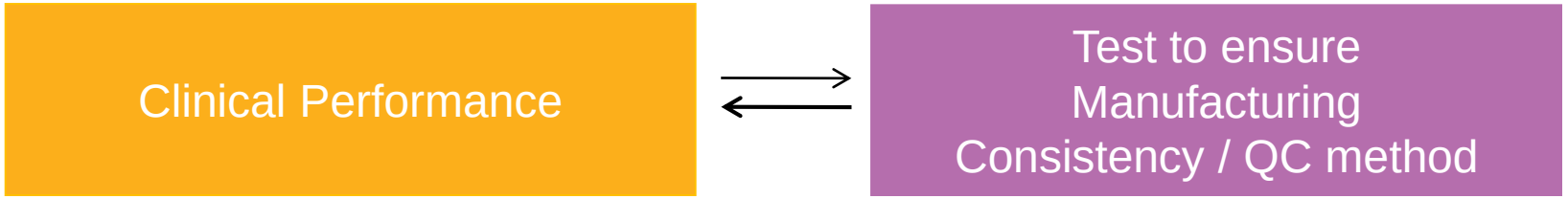
Pharmaceutical Quality in the 21st Century
Janet Woodcock, M.D.
Deputy Commissioner of Operations
5th October 2005

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

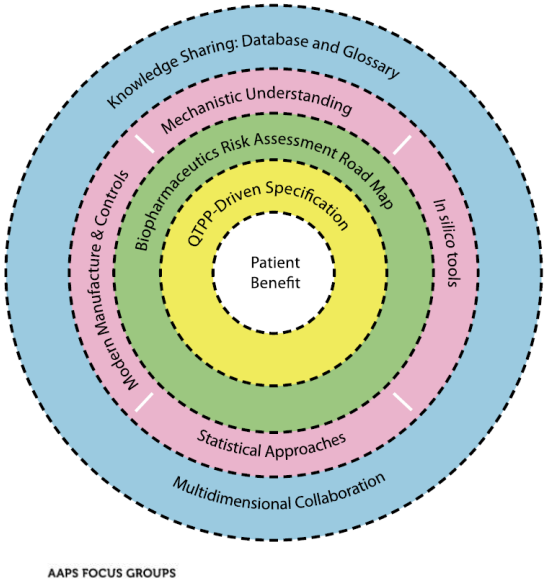
- cGMPs for the 21st century and ICH Q8 opened up of the opportunity for a lot of discussion about quality and focus fell on the dissolution test



- **The design space/control strategy needs to deliver the correct dissolution performance**
- Whole bunch of workshops on this matter e.g.:
  - AAPS workshop: Challenges for Dissolution Testing in the Twenty-first Century: Linking Critical Quality Attributes and Critical Process Parameters to Clinically Relevant Dissolution (2006)
  - AAPS Workshop: Role of Dissolution in QbD and Drug Product Life Cycle (2008)

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
- FDA sponsored meeting: Applied Biopharmaceutics and Quality by Design for Dissolution/Release Specification Setting: Product Quality for Patient Benefit (2009)
- As well as a focus on clinically relevant dissolution specifications there is movement that puts patients at the centre of drug product development



Selen A, Cruañes MT, Müllertz A, Dickinson PA, Cook JA, Polli JE, Kesisoglou F, Crison J, Johnson KC, Muirhead GT, Schofield T, Tsong Y. Meeting report: applied biopharmaceutics and quality by design for dissolution/release specification setting: product quality for patient benefit. AAPS J. 2010;12:465–72. doi:10.1208/s12248-010-9206-0.

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:

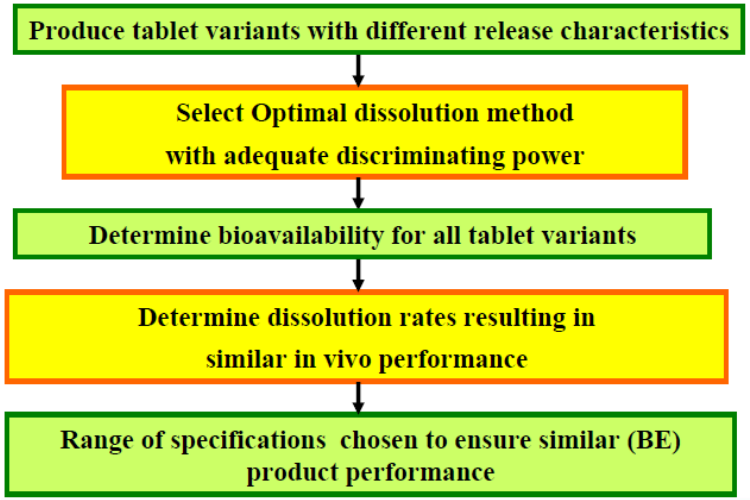
- Intended use in clinical setting, route of administration, dosage form, delivery systems;
- Dosage strength(s);
- Container closure system;
- Therapeutic moiety release or delivery and attributes affecting pharmacokinetic characteristics (e.g., dissolution, aerodynamic performance) appropriate to the 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.



Step	Example
1. Conduct Quality Risk Assessment (QRA)	QRA to allow the most relevant risks (product and process variables) to *in vivo* dissolution to be identified (ICH Q9)
2. Develop appropriate CQA tests	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)
3. Understand the *in vivo* importance of changes	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
4. Establish appropriate CQA limits	Establish the *in vitro* dissolution limit that assures acceptable bioavailability.
5. Use the Product Knowledge in Subsequent QbD steps	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).

Dickinson et al. (2008) AAPS Journal. 10: 380-90

Suarez-Sharp: http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/UCM301057.pdf

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)

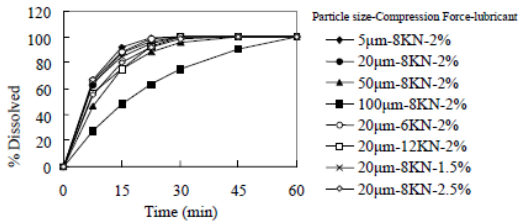


Figure 2.3.P.2.3-2 Dissolution Profiles from Tablets with Varied Drug Substance Particle Size (D90 Compression Force and/or Lubricant Amount

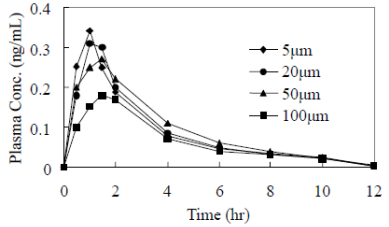


Figure 2.3.P.2.3-3 Blood Concentration Profiles

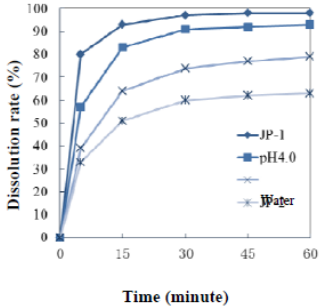
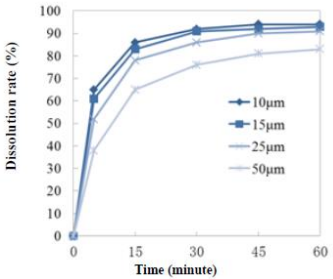


Figure 2.3.P.2.2-1 Dissolution profile of the proposed drug product



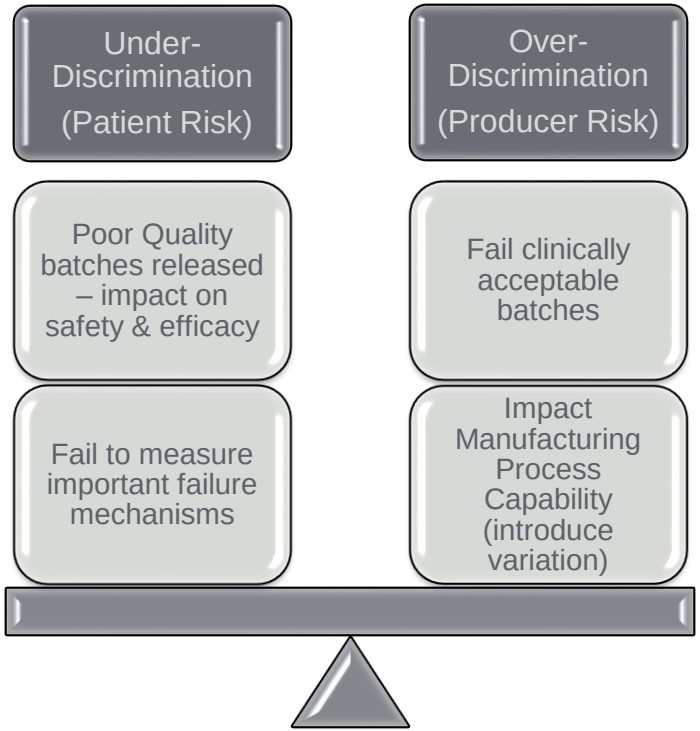
(b) Dissolution (pH 4.0, 50 rpm)

http://www.nihs.go.jp/drug/DrugDiv-E.html

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

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

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

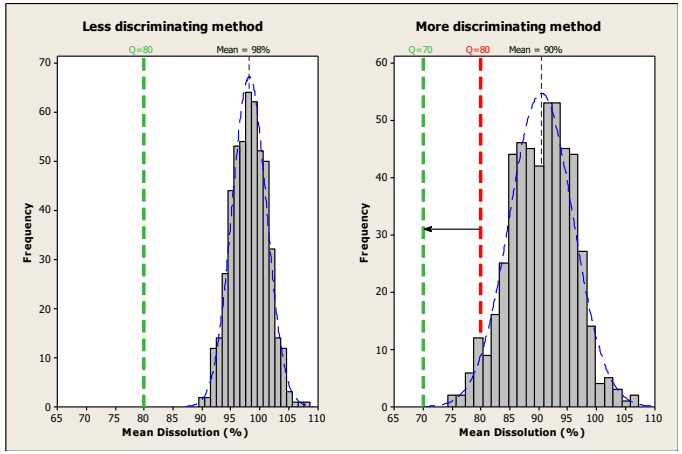
Discriminatory power and complete release vs process capability

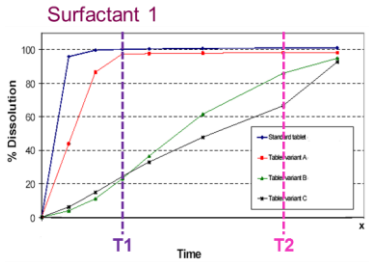
- A discriminatory dissolution method without a clinically relevant specification can reduce process capability and potentially impact security of supply.
- Setting the specification only on development data, when the full spectrum of commercial process variation has not been experienced[1], can lead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

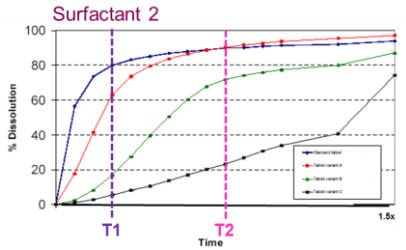
[1] Process Validation: General Principles and Practices . US FDA Guidance for Industry; 2011.

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



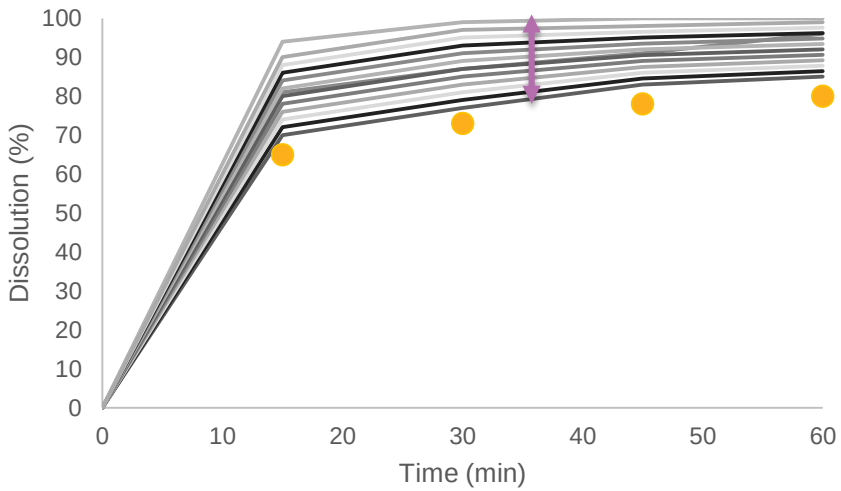




f2 testing with a clinically relevant method and specification to support post-approval changes

- 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

Simulated date representing potential batch variability with a discriminatory method:



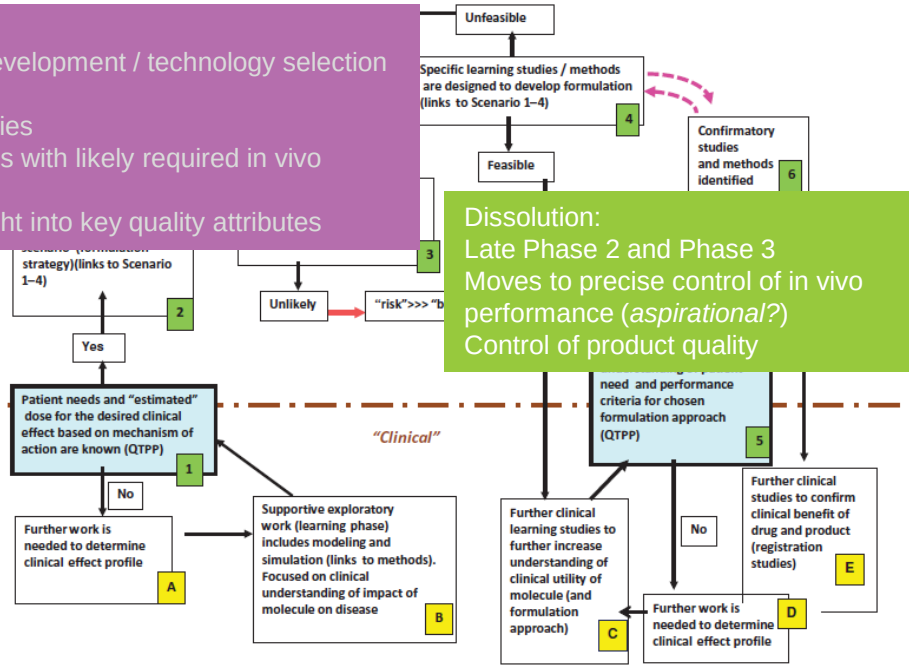
- ↕ f2 ~ 35
- > ● = clinically acceptable batch

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

ARZU SELEN,[1] PAUL A. DICKINSON,[2] ANETTE MÜLLERTZ,[3] JOHN R. CRISON,[4] HITESH B. MISTRY,[5] MARIA T. CRUAÑES,[6] MARILYN N. MARTINEZ,[7] HANS LENNERNÄS,[8] TIM L. WIGAL,[9] DAVID C. SWINNEY,[10] JAMES E. POLLI,[11] ABU T. M. SERAJUDDIN,[12] JACK A. COOK,[13] JENNIFER B. DRESSMAN[14]

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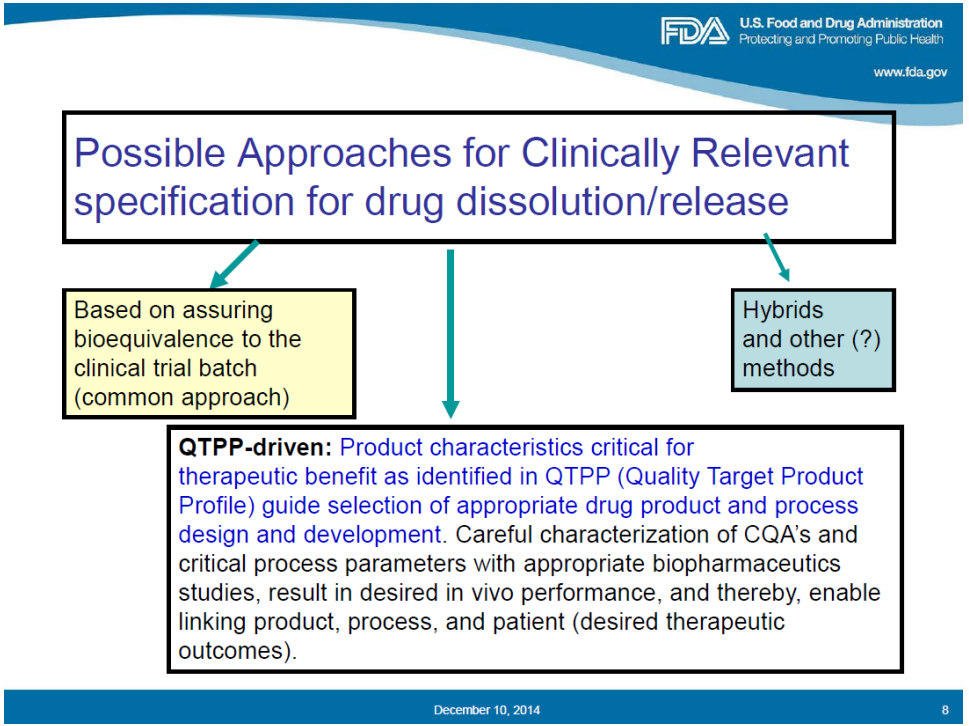
[13]Pfizer Inc., Groton, Connecticut
[14]Institute of Pharmaceutical Technology Biocenter, Johann Wolfgang Goethe University, Frankfurt, Germany

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

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.

BioRAM: an example of a more holistic approach to developing clinically relevant CQAs

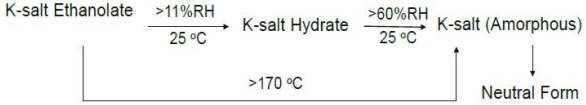
- Product design and dissolution with a specific patient need in mind: product for migraine

Scenario 1 – Rapid Therapeutic Onset

Box 4– Refined Formulation Studies

Specific learning studies / methods are designed to develop formulation

- 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!

J Pharm Sci 103, 1811-1818, 2014

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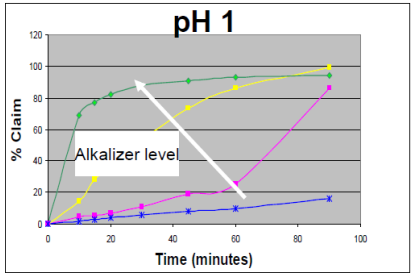
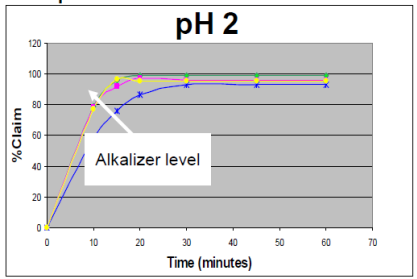
Scenario 1 – Rapid Therapeutic Onset

Back to Box 4

Arginine Alkalizer level:
Tablet Dissolution at Gastric pH*

Specific learning studies / methods are designed to develop formulation





→ At pH 1, the greater the alkalizer level, the faster the dissolution

→ At pH 2, impact of alkalizer level is less pronounced

J Pharm Sci 103, 1811-1818, 2014

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

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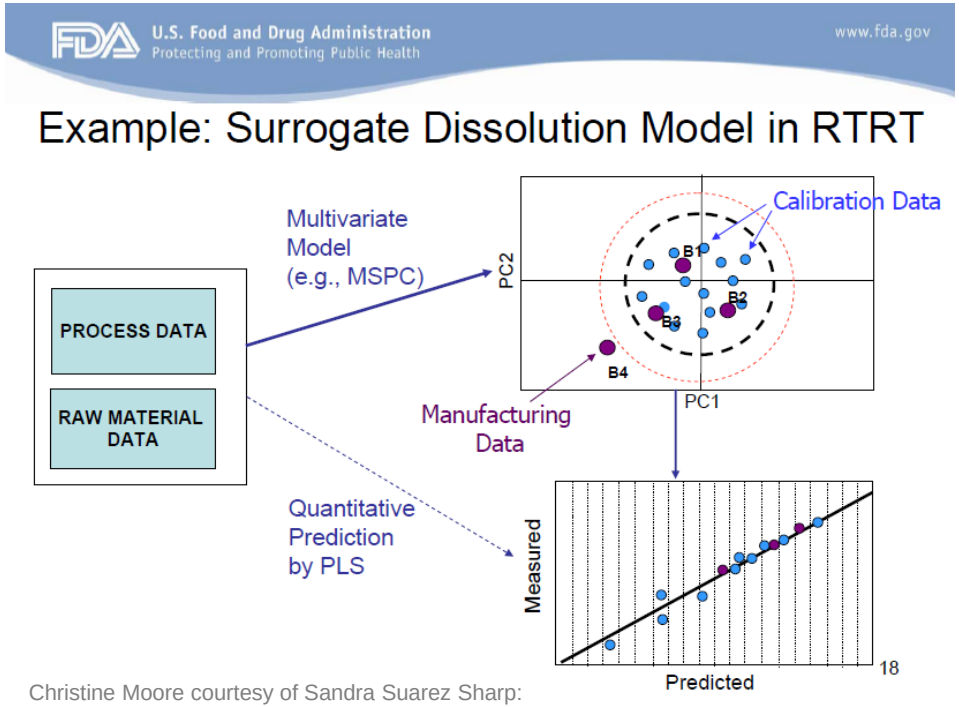
Real Time Release Testing: “wot no dissolution”

- 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: http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/UCM359262.pdf

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

Pharmaceutical Development Services