Clinically Relevant Specifications (CRS):
A Regulatory Perspective

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Outline

• Working definitions
• The problem
• Clinically relevant dissolution as an example
• Benefits of and challenges to CRS
• It’s not as simple as it looks
• Where do we go from here
  – Potential for dissolution standards
• Summary
• Conclusions
Working Definitions

• Clinically Relevant Specifications (CRS)
  – Test methods and acceptance criteria that identify and reject drug product batches that are likely to perform inadequately in the indicated patient population(s).

• Adequate clinical drug product performance
  – Appropriate pharmacological action and safe performance for a given drug, indication, and patient population(s) as claimed in the labeling.
Working Definitions

• Equivalent Quality
  – Equivalence between a reference and test drug product based on meeting in vitro specifications and any relevant in vitro bridging studies

• Bioequivalence
  – Equivalence between a reference and test drug product based on drug independent criteria of pharmacokinetic performance (e.g., Cmax, Tmax, AUC, etc.)
Working Definitions

• Clinical equivalence
  – Equivalence between a reference and test drug product based on drug dependent criteria of clinical performance (safety and efficacy) for the label claimed dose(s) in the indicated population(s)
  • Additional considerations
    – Inter-patient (population)
    – Intra-patient (individual)
Description of the Problem

- End product quality testing is largely based on limited pre-approval in vitro performance of clinical, development, pilot, commercial and stability batches.
- At initial approval, is there enough clinical knowledge to link variability in quality and specifications to adequate clinical performance?
- There are also industry, regulatory, professional, and societal expectations of quality (standards).
This Problem Results in a Tug of War

Clinical Relevance

F1 + F2 + F3 = 0

Clinical Batches

Approval Zone

Manufacturing History and Quality Standards
• Generally speaking, clinically relevant input to setting specifications is based on relatively sparse pre-approval clinical batch data.

• Clinical batch performance may differ from commercial batch performance based on:
  – Changes in site, scale, process, equipment, etc.

• Pre-approval, it is often unclear how much that matters
  – Current approaches to bridging lack flexibility and specificity in terms of clinical relevance.

• Resistance to change is our common cultural trait
This is Not a New Problem.

- Asking end product testing to adequately serve as a quality control AND as a clinically relevant surrogate has always been a challenge
- Dissolution testing and specification setting is just one example
Chemist Joseph Levine is shown around 1957 operating an “artificial stomach,” which employed liquids simulating those in the stomach and intestinal tract to measure the dissolution rate of sustained release tablets.
Clinically Relevant Dissolution 1960 (Levy-Hayes)
Clinically Relevant Dissolution 1960 (Levy-Hayes)

- Absorption rates and local irritation are interrelated and they are a function of the dissolution rate.
- Significant differences in dissolution rate exist between brands.

- What has evolved since then in terms of analytical technology, clinical relevance, and other tools?
Today: Additional Tools

- IVIVC
- BCS
- Various guidance documents
- Modeling / prediction software
- Lots of research, data, and publication
- But….
  - Change and implementation of clinical relevance has been slow by comparison to industries where relevant change yielded progress and prosperity.
Benefits of CRS

• Reject batches with inadequate in vivo performance
  – Failure to meet specifications means more likely to be clinically relevant
  – Follow up actions better clarified
  – Specifications less likely to be over or under discriminating

• Related in vitro quality standards are more likely to be clinically meaningful

• Encourages other advances and innovation
  – QbD more strongly linked to clinical relevance.
    • Especially so when dissolution is part of design space
  – Post-approval changes meaningfully linked to performance
Challenges to Develop and Implement CRS

• Multicultural resistance to change
• At initial approval there is often not enough data to identify and/or support CRS
• Balance of opportunity costs and gains
A and B are not BE

Non-clinically relevant dissolution specification (Q=80 at 30 min)

Clinically relevant dissolution specification (Q=75 at 15 min)
It’s Not as Simple as it Looks - 2

Q80% in 45 min
or
Q80% in 30 min?
It depends….

Are all 4 batches bioequivalent; or rather do they provide adequate in vivo performance?
Consider these SIMULATED DISSOLUTION profiles for individual dissolution of reference and test units.

It’s Not as Simple as it Looks - 3
It’s Not as Simple as it Looks - 4

SIMULATED plasma profiles where:

\[ Ka = 0.046 \text{ 1/min} \]
\[ Ke = 0.012 \text{ 1/min} \]
\[ t_{1/2} = 60 \text{ min} \]

Add 20% random patient variability on Ka and Ke.

*Is there clinical and/or bioequivalence?*
Where do we go from here?

• Quality standards based on known clinical risks
  – Some already exist or are being developed (safety relevance)
    • Genotoxic impurities
    • VOC’s
    • Implementation challenges persist
  – Some need updating to better account for safety and efficacy relevance
    • Content Uniformity
  – Some are waiting to be developed
Where do we go from here?

• E.g., Dissolution… *An Idea as a set of questions*
  – Is it feasible to define clinically relevant risks and designate risk categories (e.g., low, med, high)?
  – Can in vitro quality standards be set for low risk?
  – Can criteria for disintegration be developed for low risk?
  – Can we define low risk?

  – *For higher risk categories, should we consider*…
    • *More bio relevant media and conditions during development*
    • *For poorly soluble drugs consider non-sink methodologies*
Attributes of a Low Risk Case for Dissolution

- Immediate release oral solid dosage form
- Non-narrow therapeutic index drug
- Not a titrated drug
- BCS Class I or III
- Not a steep dose – response curve
- Clinical practice does not include therapeutic monitoring
- Tmax not critical (e.g., no claim of rapid onset)
- Standard media and conditions appropriate for BCS-I and III
- Other
Summary

- There are many benefits to CRS
  - Reject batches with inadequate in vivo performance
  - Less likely to be over or under discriminating
  - May lead to more clinically meaningful quality standards
- There are also challenges to implementing CRS
  - Technical hurdles in developing functional models
  - Lack of sufficient relevant CRS data at initial approval
  - Cultural resistance to change
  - Investment costs not seen to translate to benefit
Conclusions

• CRS are needed in the modern world
• The benefits of CRS are worth investing in
• Compartmentalizing the problem on a risk basis can facilitate progress
  – An approach for a low risk case illustrates possibilities
• CRS will exploit and in turn further stimulate other advances such as QbD
  – Consider more supportive data to support CRS at initial approval
    • product, development, and quality system designs
    • IVIVC for MR products, etc.
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