Quality by Design and Clinical Relevance: Moving Forward - Clinical Pharmacology Considerations

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Outline

• Acknowledgments
• Clinical Relevance (CR)
• CR in Clinical Pharmacology (CP)
• Examples
• CR and CP in Biopharmaceutics (BP)
• Additional Considerations
• Summary
DISCLAIMER

• Views expressed are mine and do not reflect official FDA Policy.
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ACKNOWLEDGEMENTS

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Clinical Relevance

**Definition:** Clinical Relevance = within acceptable Benefit / Risk Framework

**Endpoints:**

- **Pharmacodynamic (PD)** - Efficacy Endpoints, safety endpoints, surrogate endpoints, mechanistic biomarkers, panel of biomarkers, ‘fit for purpose’ biomarkers
- **Pharmacokinetic (PK)** – various drug exposure metrics

**Measurement variability / ability to detect difference:**

Manufacturing variables > PK measures > PD measures > Compliance
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CR in CP

- **Central construct in CP is the Exposure – Response framework**

- **Exposure** is dose or any informative PK measure
- **Response** is all informative PD (efficacy AND safety) measures

- Impact of all extrinsic (e.g., DDI, food effect) and intrinsic (e.g., genetic polymorphism, organ impairment) factors on exposure metrics is interpreted WRT to the E – R framework
CR in CP

• Absence of a well characterized E – R framework leads to the typical current Bioequivalence (BE) confidence interval (CI) limits of 80-125%, which typically don’t allow more than ~12% difference in exposure between Test and Control
CR in CP

• A well characterized shallow E – R framework can allow acceptance of much wider CI limits, i.e., a multifold difference in exposure between Test and Control

• Steep E – R framework is uncommon but when identified, it can lead to tightening of the typical CI limits
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Example 1: Dabigatran
(data presented is in public domain)
Example 1: Dabigatran

- E - R relationship evaluation of dabigatran highlighted a steep exposure-ischemic stroke and exposure-life threatening bleeding relationship.
- Little separation between dabigatran plasma concentrations that lead to therapeutic failure or serious adverse effect.
- Additionally, dabigatran has high within subject variability, primarily due to its poor oral bioavailability which normally can invoke ‘reference scaling’ approach for BE determination.
- Steep exposure – response finding was key for the OGD dabigatran BE guidance to be revised from a reference scaling approach to average BE approach.
- Not desirable to have generic dosage form further add to this high variability.
Example 1: Dabigatran

Additional Comments in the OGD Draft Guidance:

- Dabigatran demonstrated a steep exposure-response relationship for both efficacy and safety. Therefore applicants should not use the reference-scaled average bioequivalence (BE) approach to widen the BE limits for dabigatran BE evaluation.
- Applicants should use the average BE approach, with BE limits of 80-125%.
- The within-subject variability of test and reference products should be compared and the upper limit of the 90% confidence interval for the test-to-reference ratio of the within-subject variability should be ≤ 2.5.
Example 2: Apixaban
(data presented is in public domain)

<table>
<thead>
<tr>
<th>Population Description</th>
<th>PK Parameter</th>
<th>Fold Change and 50% CI</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strong CYP3A4/P-gp inhibitor:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ketaconazole 400 mg</td>
<td>Cmax</td>
<td>Reduce dose by half</td>
<td></td>
</tr>
<tr>
<td></td>
<td>AUC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other CYP3A4/P-gp inhibitors:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diltiazem 360 mg</td>
<td>Cmax</td>
<td></td>
<td>No dose adjustment</td>
</tr>
<tr>
<td></td>
<td>AUC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Naproxen 500 mg</td>
<td>Cmax</td>
<td></td>
<td>No dose adjustment</td>
</tr>
<tr>
<td></td>
<td>AUC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Strong CYP3A4/P-gp inducer:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rifampin 500 mg</td>
<td>Cmax</td>
<td></td>
<td>Avoid concomitant use of Strong CYP3A4/P-gp inducers</td>
</tr>
<tr>
<td></td>
<td>AUC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other agents</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Famotidine 40 mg</td>
<td>Cmax</td>
<td></td>
<td>No dose adjustment</td>
</tr>
<tr>
<td></td>
<td>AUC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atencol 100 mg</td>
<td>Cmax</td>
<td></td>
<td>No dose adjustment</td>
</tr>
<tr>
<td></td>
<td>AUC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enoxaparin 40 mg</td>
<td>Cmax</td>
<td></td>
<td>No dose adjustment</td>
</tr>
<tr>
<td></td>
<td>AUC</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Example 2: Apixaban

Setting the exposure lower bound:

Table 8 Event rate and hazard ratio for primary efficacy endpoint in 2.5 mg and high body weight subgroup.

<table>
<thead>
<tr>
<th></th>
<th>Median Apixaban AUCss (ng*hr/mL)</th>
<th>Apixaban n/N (% yr)</th>
<th>Warfarin n/N (% yr)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.5 mg</td>
<td>2703 (n = 128)</td>
<td>12/428 (1.70)</td>
<td>22/403 (3.33)</td>
<td>0.50 (0.20-1.02)</td>
</tr>
<tr>
<td>Weight ≥120kg in 5 mg</td>
<td>2690 (n = 179)</td>
<td>4/513 (0.40)</td>
<td>12/519 (1.19)</td>
<td>0.34 (0.11-1.06)</td>
</tr>
<tr>
<td>Weight &lt;120kg in 5 mg</td>
<td>3662 (n = 2625)</td>
<td>196/8179 (1.30)</td>
<td>231/8159 (1.55)</td>
<td>0.84 (0.70-1.02)</td>
</tr>
</tbody>
</table>
Example 2: Apixaban

Setting the exposure lower bound:

- The median Apixaban exposure in patients with high body weight receiving the 5 mg dose was similar to that in the 2.5 mg.
- In both groups, concentrations are ~25% lower compared to the average 5 mg dose group.
- There was robust effect in reducing stroke/SE in both, the 2.5 mg and the high body weight group compared to Warfarin.
- These results indicated that 25% decrease in Apixaban exposure due to any intrinsic or extrinsic factor likely will not result in loss of efficacy.
Example 2: Apixaban

Setting the exposure upper bound

Figure 8: Probability of ISTH Major bleeding within 1 year as a function of the AUCss for apixaban. The shaded region represents the 95% confidence interval. The bars on the bottom represent 5th to 95th percentiles of apixaban AUCss by dose subgroup in the ARISTOTLE PK subset.
Example 2: Apixaban

Setting the exposure upper bound:

- A Cox Proportional Hazard model was used to study relationship between AUCss and time to first major bleed while controlling for potential covariates. Nearly 12,000 patients were included in the analysis.
- Age, serum creatinine, body weight, prior stroke/TIA/SE, aspirin use were identified as significant risk factors and included in the model.
- After adjusting these covariates, the positive relationship between AUCss and risk of ISTH major bleeding remained significant.
- Doubling of exposure (AUCss) led to ~75% increase in bleeding risk.
- Increases in exposure up to ~40% had acceptable risk in phase 3 trials.
- Dose reduction could occur only by half due to two strengths – 2.5 mg and 5 mg.
Example 2: Apixaban

<table>
<thead>
<tr>
<th>Population Description</th>
<th>PK</th>
<th>Fold Change and 90% CI</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Renal impairment:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe (CrCl=15-29 mL/min)</td>
<td>Cmax, AUC</td>
<td></td>
<td>No dose adjustment</td>
</tr>
<tr>
<td>Moderate (CrCl=30-50 mL/min)</td>
<td>Cmax, AUC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mm (CrCl=51-80 mL/min)</td>
<td>Cmax, AUC</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Age:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;= 65 years</td>
<td>Cmax, AUC</td>
<td></td>
<td>No dose adjustment</td>
</tr>
<tr>
<td><strong>Body weight:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;= 120 kg</td>
<td>Cmax, AUC</td>
<td></td>
<td>No dose adjustment</td>
</tr>
<tr>
<td>&lt;= 50 kg</td>
<td>Cmax, AUC</td>
<td></td>
<td>No dose adjustment</td>
</tr>
<tr>
<td><strong>Hepatic impairment:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild (Child-Pugh A)</td>
<td>Cmax, AUC</td>
<td></td>
<td>No dose adjustment</td>
</tr>
<tr>
<td><strong>Gender:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>Cmax, AUC</td>
<td></td>
<td>No dose adjustment</td>
</tr>
</tbody>
</table>

Change relative to reference
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CR and CP in BP

• Current goalposts in BP and optimization within these goalposts

• Possible expansion of these goalposts
CR and CP in BP

Current goalposts in BP and optimization within these goalposts:

• Normal BE criteria, i.e., 90% CI limits of 80-125% are used as the goalposts for managing all manufacturing changes, e.g.:
  – SUPAC IR
  – SUPAC MR
  – IVIVC

• Optimization can occur even within and using these goalposts, e.g.:
  – Wider specs based on IVIVC
  – BCS classes, IVIVR / IVIVC and ‘safe space’
  – Greater flexibility in dissolution specs for BCS Class 1 and 3 products
CR and CP in BP - Example relationship between dissolution and absorption

- IVIVC
- IVIVR (Safe Space)
- Mixed safe space / IVIVC

Gastric emptying/
Permeability
Rate limiting

Change in $C_{max}$ or AUC (%)

Time to x% dissolution (min)
CR and CP in BP

- Regulatory flexibility for well-behaved IR products, e.g., BCS Class 1 and 3; proposed in the draft dissolution guidance for BCS Class 1 and 3 products.
CR and CP in BP

Possible expansion of these goalposts:

• A product with a well characterized non-steep / shallow E-R framework developed using clinically relevant response variables, may be considered for widening the conventional BE goalposts.

• For such a product, characterize the in-vivo consequence of the formulation / manufacturing ‘failures’

• Interpret clinical relevance of these in-vivo findings using the above stated E-R framework.

• Create your own SUPAC!
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Additional Considerations

• Explore new ideas, e.g., revise the IVIVC guidance using new tools like PBPK?!
• Collaboration:
  – OrBiTo consortium in Europe consisting of industry, academia and regulatory agencies, with dedicated funding provided via the Innovative Medicines Initiative (IMP), and matched by industry.
  – PQRI initiative in USA; recent PQRI workshop
• Ease / difficulty in assuring Compliance
• Education / training of Agency and industry scientists on new guidances and developments
CR and CP in BP
OrBiTo Mission Statement

“Through partnership, collaboration and data sharing, we will develop, validate and implement a suite of biopharmaceutics tools applicable throughout the drug development process. By developing our fundamental knowledge of the gastrointestinal environment, we will deliver innovative tools to accurately predict product performance over a range of clinically relevant conditions. The integration of *in vitro* and *in silico* approaches will provide a biopharmaceutics toolkit, validated using clinical data, to accelerate drug development.”

*OrBiTo is a Research consortium between EU and european Industry (EFPIA) within the Innovative Medicines Initiative (IMI)*

*5 year project with 25 million Euro budget (half EU funding, half Industry in-kind)*
PBPK based IVIVC – a logical next step in context of development and biowaivers

PBPK

Based on physiological understanding modelling and first principle modelling

Take into account how other absorption factors influences effect of dissolution

⇒ Greater confidence in IPD/PBPK based biowaivers

⇒ Possibility for biowaivers for all type of products, not only controlled release

Classic IVIVC

Based on empirical mathematical models

Assumes dissolution proportional to absorption

Apply same criteria for validation prior to use for biowaivers

Guidance for Industry

Extended Release Oral Dosage Forms: Development, Evaluation, and Application of In Vitro/In Vivo Correlations
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Summary

1. CP assessments are made based on a well characterized exposure (dose / PK) – Response (efficacy and safety measures) framework.

2. In absence of this E – R framework, the typical ‘no effect’ boundaries are the current BE limits, i.e., CI of 80-125%

3. Even within the BE limits / goalposts of 80-125%, there is very good scope of setting ‘liberal’ specifications based on approaches like BCS and IVIVR
Summary

4. Expanding the current goalposts (80-125%) to set clinically relevant specs can be approached by utilizing a robust E – R framework developed for the product

5. Compliance considerations should be carefully thought through in such situations

6. Existing guidances (e.g., IVIVC) should be updated utilizing new methodology and state-of-the-art science
Thanks!