FDA’s Experience on IVIVC-New Drug Products

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Outline

- The Purpose of IVIVC
- FDA’s Experience in IVIVC
  - Type of submissions
  - Type of dosage form
  - Type of correlations
  - Type of modeling approaches
- Key Aspects on the Development of an IVIVC
- Examples of Common Causes of IVIVC Failure
- Regulatory Applications of IVIVCs
- Overall considerations on IVIVC and Conclusions
The Purpose of IVIVC

- Reduction of regulatory burden: IVIVC in lieu of required *in vivo* studies, leading to:
  - Time/Cost savings during product development
    - Less testing in humans

- Permits setting wider than standard (±10%) *in vitro* release acceptance criteria
Integration of IVIVC into QbD

IVIVC can provide:

- Supports approval of a design space
  - Prediction/determination of the clinical impact of “movements” within the design space without the need for additional in vivo studies

- Enhanced significance of in vitro testing
  - Permits the setting of acceptance criteria based on targeted clinically relevant plasma concentrations

- Wider drug product acceptance criteria resulting in regulatory flexibility
Why is the Use of IVIVC Relevant During QbD Implementation?

- IVIVC enhances drug product understanding during development because without it, it would be impractical to define the \textit{in vivo} impact of each component and manufacturing step through \textit{in vivo} studies.

- Dissolution testing and plasma drug concentrations are identified as the most successful surrogate for safety and efficacy.
The USFDA IVIVC Guidance*

- Describes the characteristics of the raw data needed for the construction of an IVIVC (e.g., study design)

- Gives recommendations on model development

- Describes the evaluation of model predictability

- Describes which manufacturing changes can be filed with an IVIVC

Type of Regulatory Submissions Containing IVIVC Models (2009-2012)

- NDA: 89%
- IND: 11%

N=36
Type of Formulations Containing IVIVC Models (2009-2012)

- ER: 86%
- IR: 8%
- IR/ER: 6%

N=36
Type of Dosage Form Containing IVIVC Model (2009-2012)

- Oral dosage form: 69%
- Other (e.g., drug/device combos): 25%
- IM suspension: 6%

N=36

Principles described in the IVIVC guidance are applicable to other dosage forms
IVIVC Categories: NDA/IND Submitted (2009-2012)

- Level A: 74%
- Level B: 3%
- Level C: 8%
- Other: 15%

N=36
Types of Modeling Approaches Included in Regulatory Submissions (2009-2012)

- Two-Stage Independent: 67%
- One-Stage Direct Convolution: 18%
- One-Stage Compartmental Approach: 9%
- Other: 6%

N=36
Types of Dissolution Media Used in IVIVC (2009-2012)

- pH 1.2 Buffer, Simulated Gastric TS (without pepsin)
- 0.01N HCL with 0.05% SLS and 0.7% NaCl
- 0.04 M sodium phosphate buffer pH 6.8 containing 2% SLS
- Water (drug product has condition independent dissolution)
- 0.05 M Sodium Citrate and 0.09 N NaOH, pH 4.8. At 5 hours, pH is adjusted to 6.6 with addition of 100 mL media: 0.05M sodium phosphate and 0.46N NaOH
- Ethanol/water 90/10 v/v (%)

Successful IVIVC models are also possible when simple dissolution methods (USP listed) are used
What Are the Key Aspects of the Development of an IVIVC?
Key Aspects of an IVIVC

- Robustness of the correlation as proven by:
  - Meeting the criteria for internal and external predictability

- Meeting the criteria for *in vitro, in vivo* experimentation
  - Number and in vitro release rate characteristics of formulations used in the construction of the model
  - Rank order correlation
  - Fasting conditions

- The use of individual concentrations in the deconvolution process (model independent approach)
Examples of Common IVIVC Issues
No Difference in the in Vitro Release Rate Characteristics

Formulations should have different release rate characteristics

<table>
<thead>
<tr>
<th>Formulations</th>
<th>f2</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>B</td>
</tr>
<tr>
<td>A</td>
<td>C</td>
</tr>
<tr>
<td>B</td>
<td>C</td>
</tr>
</tbody>
</table>
Lack of Rank Order Correlation

Data should show a rank order correlation

<table>
<thead>
<tr>
<th>Formulations</th>
<th>f2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fast</td>
<td>medium</td>
</tr>
<tr>
<td>Fast</td>
<td>slow</td>
</tr>
<tr>
<td>medium</td>
<td>slow</td>
</tr>
</tbody>
</table>

Medium and fast were BE
Formulations Do Not Have the Same Scaling Factor

Form A, $s_l=0.39$

Form B, $s_l=1.3$

Form C, $s_l=0.93$

All formulations should use the same Scaling factor
Other Causes for IVIVC Failure

- IVIVC model did not meet validation criteria
- Use of mean-based deconvolution instead of individual-based deconvolution
- Model developed under fed conditions for a drug that exhibits substantial food effect
  - Fed conditions should only be used when safety
- Model is over-parameterized and not fully mechanistic
What Are the Regulatory Applications of an IVIVC?
Regulatory Applications*

- Waiver of required *in vivo* BA/BE studies:
  - Pre-approval manufacturing changes
  - Post-approval changes
  - Approval of lower strengths

- Wider than standard (±10%) *in vitro* release acceptance criteria
  - The difference in predicted means of Cmax and AUC from upper and lower release limits are no more than 20%

- Evidence for biorelevant and discriminating dissolution method
  - Setting of clinically relevant drug product acceptance criteria
  - Wider drug product acceptance criteria resulting in regulatory flexibility

Wider than Standard (±10%) in vitro Release Limits

Convolution

- Applicant's proposed ± 15%
- Target ± 10%

Fraction Dissolved

Time (hrs)

Predicted plasma concentrations (ng/mL)

Time (hrs)
Wider than Standard (±10%) in vitro Release Acceptance Criteria, cont.

<table>
<thead>
<tr>
<th></th>
<th>Cmax (ng/mL)</th>
<th>AUC (ng*hr/mL)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>% difference (high vs. low)</td>
<td>% difference (high vs. low)</td>
</tr>
<tr>
<td>Target - 10%</td>
<td>17%</td>
<td>15%</td>
</tr>
<tr>
<td>Target +10%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Applicant's low</td>
<td>19%</td>
<td>17%</td>
</tr>
<tr>
<td>Applicant's high</td>
<td></td>
<td></td>
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</table>

Dissolution acceptance criteria were set based on the mean dissolution values for the biobatch and stability batches ± 15% variation.
Support of Post-Approval Changes Requiring BE studies

<table>
<thead>
<tr>
<th>Batch #</th>
<th>Site</th>
<th>Mean Predicted Cmax (ng/mL)</th>
<th>Mean predicted AUC (ng*h/mL)</th>
<th>% Difference (Current vs. New)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Cmax</td>
</tr>
<tr>
<td>A11</td>
<td>New</td>
<td>275</td>
<td>4359</td>
<td>1</td>
</tr>
<tr>
<td>A12</td>
<td>New</td>
<td>277</td>
<td>4328</td>
<td>2</td>
</tr>
<tr>
<td>A13</td>
<td>New</td>
<td>270</td>
<td>4383</td>
<td>-3</td>
</tr>
<tr>
<td>B00</td>
<td>Current</td>
<td>274</td>
<td>4356</td>
<td>---</td>
</tr>
</tbody>
</table>

Criteria

- Predicted profiles from pre- and post change are within 20% range of AUC and Cmax
  - Supersedes f2 similarity testing
Common Mistake in the Application of the IVIVC

- Prediction of Cmax and AUC defined by the upper and lower dissolution acceptance criteria boundaries
  - If predicted values meet the acceptance criteria (less than 20% difference), then the CMC change is acceptable

- Instead, the PK predicted profiles from pre- and post change should be within 20% range of AUC and Cmax
Clinically Relevant Drug Product Specifications: A possibility even without IVIVC
Drug Product Z

- BCS 2 Drug Substance
- Immediate Release Tablet
- Single strength
- Proposed Level C and A IVIVCs
IVIVC Development/Evaluation

- Dedicated PK study to determine the effect of particle size (PS) on dissolution and BA

- Release rate was altered by changing the particle size of the drug substance

- Linear IVIVC model constructed was found not acceptable by the FDA
Making Sense of the Data

- Setting clinical relevant specifications can still be performed
  - The dedicated PK study provided enough information to determine which dissolution rates result in similar in vivo performance
    - Clinical relevancy is established for those changes whose dissolution profiles fall within the extremes of dissolution profiles for batches that were BE
Clinically Relevant PS Ranges

Batches A, B, C, D, and Clinical were BE

- **Lower bound**
- **Upper bound**

**Std approach dissolution spec:**
- Q = 80% at 15 min.

**IVIVR approach dissolution spec:**
- Q = 80% at 20 min.
Overall Considerations for IVIVCs

- IVIVC can be possible for some IR formulations
- IVIVC can be possible for other routes of administration other than oral dosage forms
- FDA does not specify the kind of modeling approaches in the construction of IVIVCs
- Successful IVIVC models can be possible when simple dissolution methods are used
Overall Considerations for IVIVCs, cont.

- For an IVIVC with major impact on the approvability of the NDA submission, firms should submit the IVIVC model during IND stage
  - Changes implemented to the Phase 3 formulation requiring BE study

- IVIVC development should be planned a priori instead of being a *post-hoc* event
  - Ensures the use of robust/appropriate analysis of the data
  - Increases the outcome of a successful correlation
Overall Considerations for IVIVCs, cont.

- Once approved, the IVIVC should be used to support pre- and post approval manufacturing changes:
  - IVIVC supersedes f2 testing
  - Pre- and post-change dissolution data should be used to predict Cmax and AUC to determine acceptability

- Clinical relevancy of the specifications for material attributes/process parameters can still be determined in the absence of an IVIVC model
  - Clinical relevancy is assured for those changes whose dissolution profiles fall within the extremes of dissolution profiles for batches that were BE
Conclusions

- FDA encourages the inclusion of IVIVC models in regulatory submissions. IVIVC models provide:
  - A direct link to in vivo performance
    - Establishment of clinically relevant drug product specifications
  - Stronger link between in vivo and in vitro performance as compared to using $F_2$ testing
    - Regulatory flexibility within the QbD frame-work