Applications of In Vitro-In Vivo Correlations in Generic Drug Development: Deficiencies and Case Studies

Paramjeet Kaur, Ph.D.
Division of Bioequivalence II, Office of Bioequivalence
Office of Generic Drugs
United States Food and Drug Administration

AAPS Symposium on Drug Dissolution in Human GI Tract: Direct Measurements and Modeling
Denver, Colorado, November 17, 2016
Disclaimer

The opinions and information in this presentation are those of this presenter and does not necessarily represent views and/or policies of the U.S. Food and Drug Administration.
Topics for Discussion

- Definition and purpose of in vitro-in vivo correlation (IVIVC)
- Role of IVIVC in generic drug development
- US-FDA IVIVC Guidance
- IVIVC data in generic drug submissions for oral drug products
- Commonly occurring deficiencies associated with IVIVCs
- Case studies
Definition of IVIVC

A predictive mathematical model describing the relationship between an in vitro property of a dosage form (e.g., in vitro dissolution) and a relevant in vivo response (e.g., amount absorbed)
Purpose of IVIVC

To establish the dissolution test as a surrogate for human bioequivalence (BE) studies, leading to

- Less testing in humans
- Reduction in regulatory burden
- Time and cost savings during product development and throughout the drug product’s life cycle
Advantages of Developing an IVIVC Early During Generic Drug Development

- Drug product formulation optimization and selection
- Risk assessment and selection of critical material attributes and process parameters
- Verification of the design space
- Establishment of biopredictive dissolution methods ensuring real-time release testing for continuous drug product manufacturing
Regulatory Applications of IVIVC in Generic Drug Development

- Level 3 SUPAC-MR changes
  - Non-release and release-controlling excipients
  - Manufacturing site
  - Process

- Complete removal of or replacement of non-release controlling excipients

- Waiver of in vivo BE study requirements for non bio-study strengths

- Support the development of a biopredictive dissolution method and set clinically relevant dissolution specifications

- Support setting wider than standard (±10%) in vitro release acceptance criteria
US-FDA IVIVC Guidance

- Defines levels of IVIVC
- Provides recommendations regarding
  - Type of data needed to develop an IVIVC
  - Evaluation of predictability
- Describes conditions under which an IVIVC can be used in lieu of in vivo BE studies
- List situations for which an IVIVC is not recommended
- Describes how to set dissolution specifications in absence and presence of an IVIVC

IVIVC Data in Generic Drug Submissions for Oral Drug Products
(January 1996 – June 2016)
Formulation Types with IVIVC

N=16

- ER: 81%
- IR/ER: 13%
- DR: 6%
Type of Changes for which IVIVC Data Submitted

- Preapproval changes: 62%
- Postapproval changes: 25%
- Exploratory: 13%

N=16
Specific Purpose of IVIVCs

- Changes to dissolution method and/or specifications: 37%
- Batch-to-batch variation in the particle size, coating weight, process changes, test product composition do not impact BE: 13%
- Waiver of higher or lower strength (s): 13%
- Guide the development of to-be-marketed formulation: 13%
- Challenge the results of a failed BE study: 6%
- Level 3 manufacturing site change: 6%
Commonly Used Dissolution Conditions in IVIVC Development

Simple dissolution methods were used in IVIVC development

- USP Apparatus I (basket) or II (paddle)
- pH 1.2 (0.1N or 0.01N HCl)
- pH 6.5, 6.8, or 7.5 (phosphate buffer)
Commonly Occurring Deficiencies Associated with IVIVCs
Submission of Incomplete IVIVC Report
Submission of IVIVC Data from

- Literature
- Summary Basis of Approval for the Reference Listed Drug (RLD) Product

or
IVIVC Development using

Generic Drug Formulation

and

Formulation from a different manufacturer
Use of inappropriate number of formulations for IVIVC development
Inadequate assessment of internal and/or external predictability
Case Studies
Case Study 1

**Purpose**
Support a level 3 manufacturing site change

**Applicant’s Approach**
- Manufactured 3 test formulations with different release rates i.e., slow, medium, and fast
- Used these formulations for in vitro dissolution and in vivo pharmacokinetic studies
- Developed a level A correlation using two-stage numerical deconvolution approach
- Obtained estimate of the unit impulse response using the plasma concentration-time data of an immediate release formulation
- Assessed internal and external predictabilities
Case Study 1 (cont.)

**FDA’s Assessment**

- Lack of rank order correlation: The fast- and slow-releasing formulations had similar dissolution profiles, despite the fact that these two formulations showed marked differences in $C_{\text{max}}$ and AUC

- Internal and external predictabilities were not confirmed

**Outcome**

Applicant conducted an in vivo study to support the level 3 manufacturing site change
Case Study 2

Purpose
Support proposed changes to dissolution method for its marketed drug product

Applicant’s Approach
- Developed a level A IVIVC using its marketed formulation and the reference product formulation
- The reference product formulation was considered as the second formulation for IVIVC development
- Did not assess internal or external predictability
Case Study 2 (cont.)

FDA’s Assessment

- Did not provide detailed information about IVIVC model development

- IVIVC development is formulation specific, therefore, it is not appropriate to use different formulations (test and reference) each from a different manufacturer

- IVIVC should be developed with formulations having different release rates, thus, use of bioequivalent formulations, i.e., test and reference having same release rate was deemed unacceptable
Case Study 2 (cont.)

FDA’s Assessment (cont.)

- Use of only one formulation may be considered for a level A IVIVC for formulations for which in vitro dissolution is independent of the dissolution test conditions
  - Did not provide evidence to show that in vitro dissolution is independent of dissolution conditions

- No internal or external predictability data submitted

Outcome

Applicant withdrew its amendment for proposed changes in dissolution method
Case Study 3

Purpose
Support change in dissolution acceptance criteria beyond the recommended range (i.e., ± 10% variation) due to a level 2 change in non-release controlling excipient

Applicant’s Approach
- Developed a level A correlation using the original test product formulation and the reference product formulation
- Used nonlinear mixed modeling approach
  - This technique models in vitro and in vivo data directly in a single stage
- Did not access internal or external predictability
Case Study 3 (cont.)

**FDA’s Assessment**

- Not appropriate to use test and reference formulations, each from a different manufacturer.

- Relationship between the in vitro dissolution and the in vivo dissolution is formulation dependent.

- In vitro dissolution rates are pH dependent for this drug product. Therefore, a minimum of 2 formulations with different release rates are required to develop IVIVC.

- No internal or external predictability data submitted.
Case Study 3 (cont.)

**Outcome**

Applicant conducted new BE studies on the reformulated test product. The dissolution acceptance criteria were then recommended based on dissolution testing conducted on the bio-lot (reformulated test product) used in the new BE studies.
Case Study 4

Purpose
Challenge the results of a failed BE study

Applicant’s Approach
- Used lower strength of the to-be-marketed (TBM) product line as fast-releasing formulation, and the higher strength as slow-releasing formulation
- Developed a level A correlation using direct convolution approach
- Assessed internal and external predictabilities
Case Study 4 (cont.)

**FDA’s Assessment**

- In vitro dissolution rates of the two formulations are similar
- In vitro dissolution of the test formulations is condition dependent
- External predictability evaluated using the formulation used in the IVIVC development

**Outcome**

Applicant conducted a new in vivo BE study, which met the BE criteria
Case Study 5

Purpose

Support changes in dissolution acceptance criteria

Applicant’s Approach

- Manufactured 3 test formulations with different release rates i.e., slow, medium, and fast
- Used these formulations for in vitro and in vivo studies
- In vitro dissolution data at different time points was correlated with the Cmax and AUC values to develop multiple level C correlations
Case Study 5 (cont.)

Applicant’s Approach (cont.)

- Developed regression equations were used to set dissolution acceptance criteria.

- To ensure that final dissolution acceptance criteria would result in formulations BE to the reference formulation, C_max and AUC were back-calculated from the final acceptance criteria limits using the regression equations.
Case Study 5 (cont.)

**FDA’s Assessment**
Confirmed that back-calculated Cmax and AUC determined using the proposed dissolution acceptance criteria met the BE criteria

**Outcome**
The Agency concurred with the proposed changes to the dissolution acceptance criteria
Conclusions/Future Direction

- Advancement in IVIVC provides an opportunity for taking a major step in model based drug development and support regulatory flexibility in drug product specifications.

- The application of IVIVC enables one of FDA’s key themes, the need for patient-centric assessment of quality in a changing world.

- Implementation of novel approaches in IVIVC (e.g., mechanistic, stochastic deconvolution) may contribute in increasing the rate of IVIVC success in regulatory submissions.
Acknowledgements

Ethan Stier, Ph.D., R.Ph., Director, FDA/OMPT/CDER/OGD/OB/DBII

Xiaojian Jiang, Ph.D., Deputy Director, FDA/OMPT/CDER/OGD/OB/DBII

John Duan, Ph.D., Acting Branch Chief, FDA/OMPT/CDER/OPQ/ONDP/DB/BBIII

Sandra Suarez Sharp, Ph.D., Acting Biopharmaceutics Lead, FDA/OMPT/CDER/OPQ/ONDP/DB/BBIII

Barbara Davit, Ph.D. J.D., Former DB II Director, Currently at Merck, Sharpe and Dohme
Thank You
Additional Case Studies
Case Study 6

**Purpose**
Support the claim that batch to batch variation in the test product composition does not impact the BE

**Applicant’s Approach**
Submitted IVIVC data from summary basis of approval (SBOA) for the RLD product

**FDA’s Assessment**
Use of IVIVC data from SBOA deemed unacceptable

**Outcome**
Applicant conducted new BE studies on the reformulated test product
Case Study 7

**Purpose**
Support change in dissolution acceptance criteria

**Applicant’s Approach**

- Developed a level A correlation using the TBM formulation and a pilot formulation
- Developed IVIVC model via the two-stage numerical deconvolution approach
- Obtained estimate of the unit impulse response using the PK data of an immediate release formulation
- Assessed internal and external predictabilities
Case Study 7 (cont.)

FDA’s Assessment

- Submitted only summary report
- No difference in the release rate of test formulations used in the IVIVC development

Outcome

Change in dissolution acceptance criteria based on additional dissolution data
Case Study 8

**Purpose**
Support the claim that batch-to-batch variation in pellet coating does not impact the BE

**Applicant’s Approach**
Submitted IVIVC data from the literature

**FDA’s Assessment**
Use of literature IVIVC data in lieu of in vivo studies was deemed unacceptable

**Outcome**
Withdrawed the submission for other reasons
Case Study 9

Purpose

Exploratory in nature

Applicant’s Approach

- Developed 2 prototype test formulations

- Evaluated these 2 prototype formulations against reference product in the pilot fasting and fed BE studies – failed to meet the BE criteria

- Used in vitro and in vivo data (from fasting study) for these 2 prototypes and reference product to build a level A correlation
Case Study 9 (cont.)

Applicant’s Approach

- IVIVC model was developed using convolution approach
- Assessed internal predictability
- Developed IVIVC model was then used to guide the development of to-be-marketed generic formulation