In Vitro-In Vivo Correlation:
Linking Drug Release to Clinical Performance

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51st Land O' Lakes Conference: Bridging Material and Product Quality in Developing Tablet Dosage Forms

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Outline

- Introduction
  - In vitro-in vivo correlation (IVIVC)
- IVIVC and Product Quality
  - Clinical linkage of in vitro drug release
  - Product and process development, understanding, manufacturing, control and changes
- Challenges and Considerations in Developing IVIVC
  - In vitro vs. in vivo
  - Drug, formulation and dissolution characteristics
    - BCS and delivery technology
    - Product design: IR, MR, FDC
  - IVIVC and BA/BE studies
- Summary

Introduction

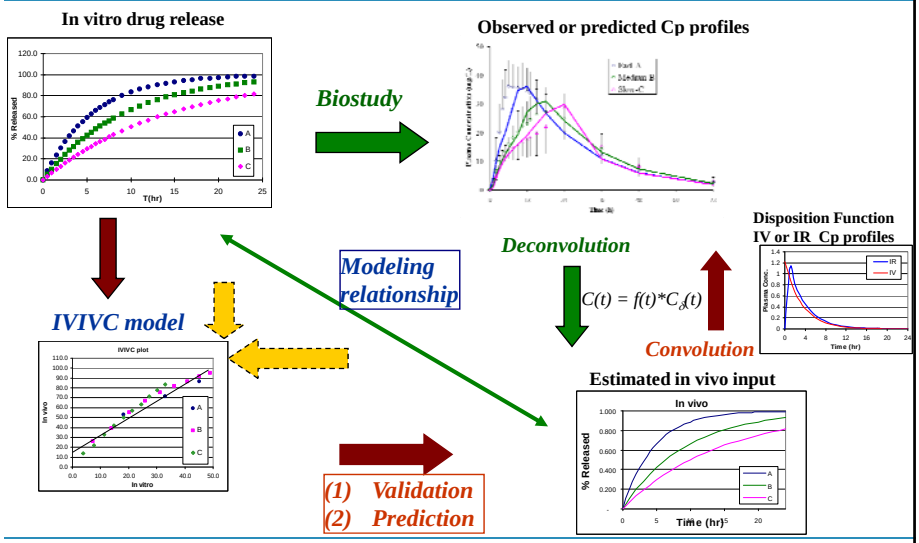
In Vitro-In Vivo Correlation (IVIVC)

- A **predictive** mathematical model describing the relationship between **an in vitro property (usually extent or rate of drug release)** and **a relevant in vivo response (e.g., plasma concentration or amount of drug absorbed)**

- Type of IVIVC
  - **Level A: Profile correlation**
  - Level B: Summary parameter correlation
  - **Level C: Characteristic parameter correlation**
  - **Multiple Level C: Multiple parameter correlation**

* ***FDA Guidance for Industry:*** *Extended release oral dosage forms: Development, evaluation, and application of in vitro/in vivo correlation. 09/1997*

Illustration: Level A IVIVC

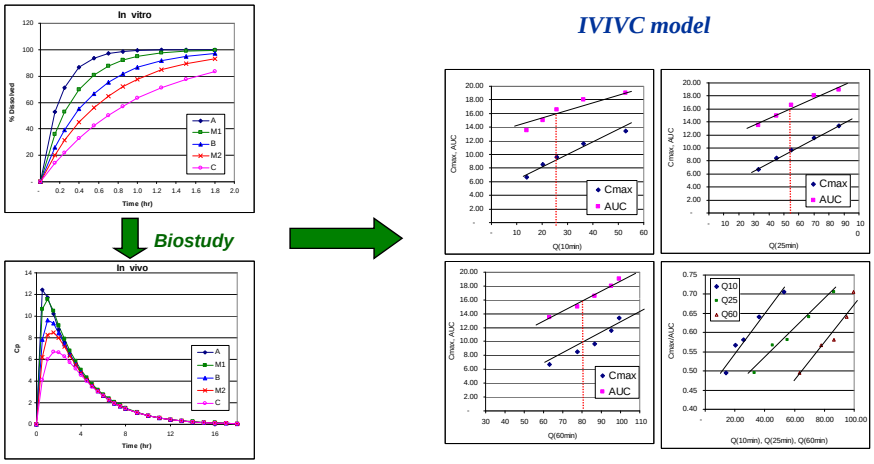


Y. Qiu. In: ***Developing Oral Dosage Forms: Pharmaceutical Theory and Practice***. Edited by Y. Qiu et al.. Academic Press, San Diego, CA. 2009. pp-379-408

Illustration: Multiple Level C IVIVC

In vitro parameters: ***Q10, Q25, Q60***

In vivo parameters: ***Cmax, AUC, (Cmax/AUC)***



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IVIVC and Product Quality

- Critical Quality Attributes (CQA)
  - Physical, chemical, biological and microbiological property that must be controlled to ensure product quality
    - Typical for solid products: Purity, potency, stability and **drug release**
- IVIVC: Clinical linkage
  - Use in vitro test to predict in vivo performance of dosage forms
    - Most common and feasible: Drug release (arbitrary ⇒ biorelevant ⇒ predictive)
  - Bridge a critical gap between product CQAs and clinical performance
    - Establish in vitro dissolution as one of the most important CQAs
      - Serve as a critical tool for product and process understanding
      - Aid product/process development, manufacturing and control
  - Provide significantly increased assurance for consistent product quality and performance under QbD
    - Predict and control clinical performance within the life cycle of a product

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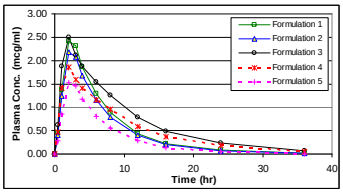
IVIVC and Product Quality

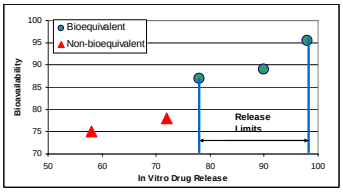
- With a validated IVIVC
  - Prior to product submission
    - Facilitate application of QbD principles in product development
    - Guide product and process design and reduce development time/cost
    - Aid scale-up, optimization and risk management
      - Assess and define CPP, design space, risks, control strategy, etc
    - Assure product quality by setting meaningful specifications
  - Post product approval
    - Justify waiver of in vivo BE studies
      - Support changes (e.g., SUPAC), variations; Reduce regulatory burden
      - e.g., IR products (BCS 2, 3, 4 drugs); MR products
    - Ensure consistent quality and performance during commercial production
      - Planned or unexpected changes/variations of raw materials, composition, process, site, equipment, etc.

IVIVC and Product Quality

- Without a validated IVIVC
  - With IVIVR
    - Map in vitro and in vivo performance
    - During development
      - Guide formulation and process screening and understanding
      - Justify biorelevant specifications
    - Post-approval
      - Ensure consistent quality of commercial products
      - Justify biowaiver
  - Without IVIVR
    - Lower confidence in using in vitro test for assuring product quality

Illustration of mapping in vitro and in vivo results





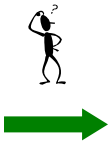
Developing IVIVC

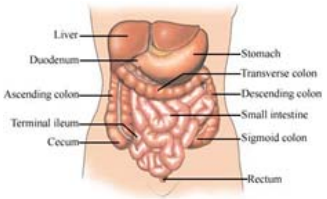
- Methodology
  - IVIVC modeling, evaluation and applications
    - Primary focus of most IVIVC colloquiums and publications over the years
    - FDA guidance and EMEA NfG published in 1997 and 1999, respectively (CPMP/QWP/604/96)
    - ***Premise:*** *available in vitro and in vivo data appropriate for establishing IVIVC*
- Data
  - Obtaining suitable in vitro and in vivo data is not a given
  - Understanding and appropriate use of the data

Challenges in Developing IVIVC

- In vitro vs. in vivo

Simple, static and controlled **Complex, dynamic and variable**





In Vivo Drug Release/absorption from Dosage Forms in the GI tract

- Estimated from availability of the drug in systemic circulation (high variability)
- *Data = f (drug properties, formulation, biological, physiological variables, and their interactions)*
  - Drug's physicochemical and biopharmaceutics properties
    - Solubility, dose, lipophilicity, permeability, ionization, physical and chemical stability, pH-dependency, IDR, solid phase, surface area, wetability, etc.
  - Biological and physiological variables
    - Transport mechanism, metabolism, transporters (absorptive, secretive), regional difference, motility, shear force, residence time, food, lumen contents, secretion, enterohepatic recycling, surface area, fluid volume, microflora etc.
  - Formulation design
    - Dosage form type, size, release mechanism, sensitivity to environmental changes, drug release kinetics and duration etc.

In Vitro Test

- Standard method
  - Pharmacopoeial methods
- Attempt to match in vivo data/simulate one or more specific GI conditions
  - Modified standard methods (hydrodynamic, shear, food…)
    - e.g., paddle+polystyrene beads; Milk; FeSSIF/FaSSIF; Two-phase; Stationary basket+Paddle; Ex-vivo fluid (aspirated human IF);…
  - New models (motility, transit, secretion, food, …)
    - e.g., Multi-vessel; Multi-compartment (TNO); Rotating dialysis cell; Flow-through cell drop method;…
- *Data = f (test method and parameters, drug properties, formulation)*

Considerations in Developing IVIVC

- Critical in achieving IVIVC
  - Feasibility
    - Understand drug properties, formulation characteristics, and their interplays with GI environment
  - Essential Condition
    - Apparent in vivo absorption
      - Dissolution rate limited
    - Relevant in vitro dosage form attribute
      - Dissolution
    - Formulations
      - Different in vivo performance
    - In Vitro Test
      - Differentiating (IVIVA, IVIVR); Predictive (IVIVC)

Immediate Release (IR) Dosage Forms: General Considerations

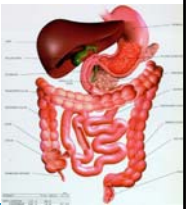
- Generally more difficult to achieve IVIVC
- Feasibility of IVIVC: API dependent
  - Apparent absorption
    - Mostly occurs in the upper intestine (often a function of many potentially confounding variables)
    - Short absorption phase in most cases (difficult to characterize for Level A IVIVC)
    - Parameters amenable to Level B, C, Multiple Level C IVIVC

IR Dosage Forms: Drug Property Considerations

- BCS Class II
  - IVIVC Possible: Dissolution rate or solubility limited absorption; Impact of formulation/process
  - *In vitro* data influenced by need for sink condition, surfactant, volume of test medium, etc.
- BCS Class I
  - IVIVC is less likely, except for:
    - Dissolution rate limiting due to formulation/process
    - BCS Borderline API
- BCS Class III
  - IVIVC rare: Gastric emptying and/or permeability is usually the rate-controlling step
- BCS Class IV
  - IVIVC is less likely: Significant competing or rate-limiting processes other than dissolution: parallel pathways, metabolism, non-linearity, etc.
  - Opportunity for IVIVR or IVIVC may exist, e.g.,
    - Both dissolution and permeability may limit the rate of in vivo absorption
    - BCS borderline API (e.g., metabolism)

Extended-Release (ER) Dosage Forms: General Considerations

- Drug release from dosage form controls drug input in the GI tract
  - Generally desirable and more likely to obtain IVIVC
  - Feasibility of IVIVC: drug molecule dependent
- Apparent absorption
  - Mostly occurs in small intestine and ascending colon or throughout
  - Longer absorption phase amenable to developing Level A, B, C or Multiple Level C IVIVC
  - Generally higher variability due to
    - A wide range of drug release and absorption environment during the traverse of the dosage form through the GI tract
  - Often influenced (confounded) by multiple variables and their interactions that are different from the “unit impulse input”



ER Dosage Forms: Drug Property Considerations

- IVIVC: Possible
  - BCS Class I
    - Dissolution rate limiting
  - BCS Class II
    - Dissolution rate limiting:
    - Release (metering) vs. dissolution (dose,/solubility, mechanism)
- IVIVC: Rare
  - BCS Class III and IV
    - Permeability rate limiting, competing processes, absorption window etc.
    - Relative rate of release to permeation (release duration, region dependent)
    - Not feasible for ER development in most cases (e.g., due to region-dependent transport)

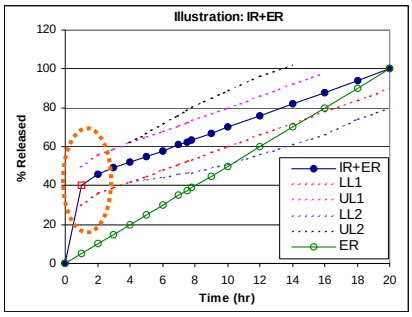
ER System: Delivery Technology Considerations

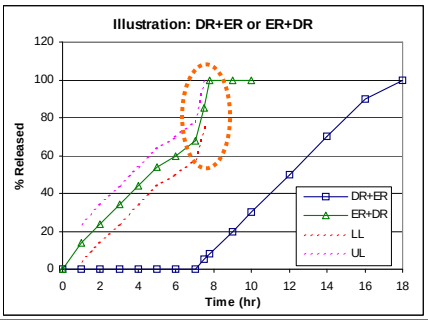
Dosage form behavior and IVIVC depends on drug property, technology and formulation design

- Osmotic Pump system
  - In vitro release generally insensitive to test conditions
  - Higher probability to obtain IVIVC
  - However
    - In vivo results depend on APIs (e.g., food effect)
    - Lack of flexibility to adjust test condition to match in vivo performance
- Reservoir system
  - In vitro release typically sensitive to in vitro test conditions
  - In vivo results depend on drug property and formulation design (e.g., food effect)
  - Possible to adjust test condition for obtaining IVIVC
- Matrix system
  - Hydrophilic matrix: Gel strength and system integrity also affect rate and mechanism of drug release
  - In vitro release sensitive to in vitro test conditions
  - In vivo results depend on drug property and formulation design (e.g., food effect)
  - Possible to adjust test condition for obtaining IVIVC

Additional Considerations: Drug Property, Product Design and Release Characteristics

- Release characteristics
  - e.g., IR/ER, ER/DR, DR/ER, FDC, …
- Formulation design and drug property (Pchem, Biopharm, PK)
  - Feasibility and IVIVC may vary with different data segment and/or API
  - Setting specification (impact on Cmax and AUC)





IVIVC and BA/BE Studies

- Development Approach
  - Retrospective
    - Review historical data from development BA/BE studies
    - Evaluate IVIVC
    - Determine the need and timing of an IVIVC study if necessary
  - Prospective (or concurrent, proactive)
    - Plan for IVIVC investigation at the start of a project
      - e.g., for BCS II drugs, MR delivery
    - Utilize data from the development BA/BE studies and start exploring IVIVC
      - If IVIVC exists, establish and validate as early as possible to facilitate product development (time, cost and resource)
      - If IVIVC doesn't exist, adjust strategy of development (risk assessment, activities and timeline)

Summary

- IVIVC
  - Linking drug release to in vivo performance: Highly desirable
    - ER product: A regulatory expectation
    - IR product: Very useful if exists
  - Facilitate rational development of product and process
  - Ensure product quality
  - Offer opportunities for regulatory flexibility
- IVIVC needs to be explored and developed on a case-by-case basis
  - There is no universal in vitro model
- IVIVC development
  - Modeling is only part of the key IVIVC components
  - Understanding API, formulation and biopharmaceutics is equally or more important
  - Proactive development can maximize opportunity and development efficiency