Using IVIVC to Manage Process Design

Russ Somma, Ph.D.

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During product development we create a store of product knowledge. The source of these data may vary but the information needed may be listed as:

- Drug substance characterization
- Process procedures
- In-process tests
- Finished product specifications
- Dissolution profiles
- Stability

These are the general categories with which we will support our product during regulatory review.

Using IVIVC Predictions to Effectively Manage Process Design

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The connection between the formulation aspects and the unit operations employed in the processing of solid oral dosage forms must be considered as a continuum during all phases of product development. While we are careful in the selection of excipient material and conduct detailed studies to assure predictable product activity the same care is not always taken when designing the associated process for conversion of the selected raw materials to finished product. The rationale at times is based upon what the regulatory impact may be rather than the potential effect on bioavailability.

Among the many challenges facing the development pharmacist is the need to assure a correlation of the in-vitro release profile of the formulation and process to the in-vivo or predicted in-vivo drug profile. This becomes more difficult when process and /or scale changes are made. Changes in key formulation components or sourcing of active pharmaceutical ingredients also contribute to confounding this requirement of assuring a consistent product that is in line with the in-vivo drug profile. The most effective tool we have in this case is the in-vitro data generated on the subject batches incorporating these aspects.

Adopting an IVIVC strategy and making it a part of the methods used to guide formulation and process development is a credible strategy that may take the following steps:

•At the product concept phase use a target in vivo profile and base in vitro specifications on an assumed IVIVC. The prototype is tested using various dissolution methods.
•The result will be a comparison of dissolution methodology with biodata allowing an IVIVC to be established.
•During optimization of the formulation / process the IVIVC is defined and predictions from the IVIVC validated.
•During scale-up the dissolution data are used to judge the impact of process changes as well establishing final specifications for dissolution.
•The database may be utilized during further scale-up and site transfer as well as supporting post approval changes.

The pharmacist may further minimize the risk factors associated with process changes by taking into account the pharmacology of the subject compound. An understanding of the compound's metabolism, absorption, and distribution may provide a roadmap to avoiding possible failure and assigning the causative factors to a less than optimal or unpredictable in-vitro/in-vivo correlation.

The discussion will center on these points as well as providing a lessons learned approach when dealing with process and formulation factors.

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These data are surfaced by employing…….

- A DOE mentality for development batches to identify parameters and interactions for all process steps.
- Establishing early stages for formulation and process steps as the basis for refinements.
- An understanding of the compound's metabolism, absorption and distribution.
  - Biopharmaceutics Classification System
  - Establish BE and/or an IVIVC
- Using pilot scale batches to further add to the knowledge base for process steps and parameters used.
- The product introduction at or near commercial scale at the launch site to further enhance the data base.

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These data would then reside in what we will label as:

1. Conventional
   - Development Reports, Stability Reports
   - Validation Protocol, Validation and Scale-Up Reports
2. Enhancements
   - Proven Acceptable Ranges
   - Quality Risk Analysis
   - Process Comparability
   - Biopharmaceutics and Clinical Pharmacology

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Process development should be used as a platform to establish proven acceptable ranges starting early in the development cycle.

Proven acceptable ranges:

- Provide a historical database for the product.
- May start at a broad range during the early stages which are subsequently tightened.
- Require a systematic reporting method which is referenced during pilot scale, scale-up and validation.
- Become a part of the knowledge store for the product and basis for statistical process control.

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Proven acceptable ranges (continued):

- Establish a chart for all process steps and controllable parameters.
- Brief description of the process step and controlled parameter.
- The engineering units which are recorded.
- The anticipated result for exceeding the proven acceptable range.
- Risk evaluation of exceeding the range is it major or minor.

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Proven acceptable ranges (continued):

- Establish the operating range to be utilized in the plant for process control.
- The proven acceptable range is documented. It may be referenced in the development report, batch records, validation reports and protocols.
- Acceptable ranges which are dependent on scale changes may be listed as to be determined (number of spray guns, FBD air volumes).

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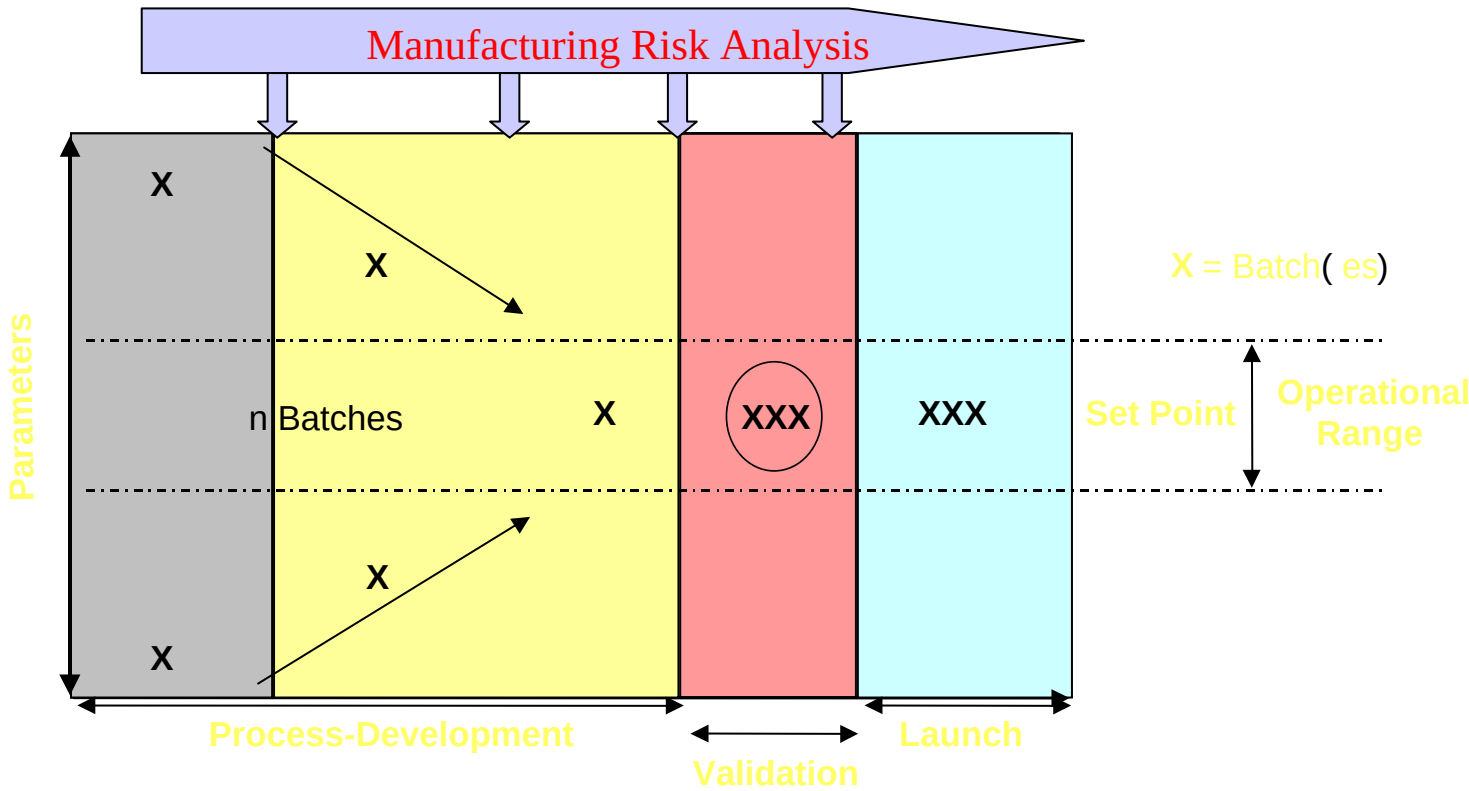

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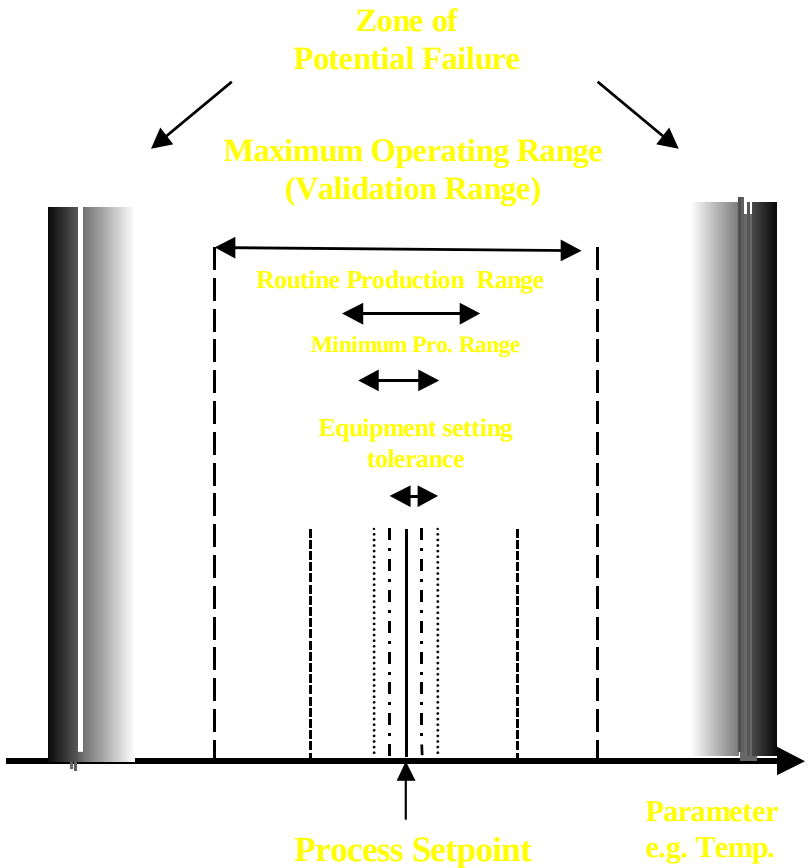

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Establish both a *good scientific* and *common sense* approach to rate each process step as having high, low or no impact on product quality.

This will aid in minimizing the subsequent validation effort (SUPAC equipment terms add clarity).

Critical area checklist:

- Weighing / addition of raw materials (vendors, personnel)
- Pre-screening (agglomeration rate, bulk density, PSD, storage conditions)
- Pre-blending of materials (volume, bulk density)
- Granulation (speed, rate of addition, time, LOD,material's physical characteristics)
- Drying (LOD, time, temperature,air volume,moisture content)

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Critical area checklist (continued):

- Particle size reduction (screen, feed rate, speed)
- Blending / lubrication (time, bulk density, assay, static charge,rotational speed)
- Compression (speed, feed rate, force applied, pre-compression)
- Coating (suspension prep., endpoint, air flow, temperature, spray rate)

This provides for subsequent data review for traits and atypical behavior. Data may be shown graphically to identify process variability within established specifications (process comparability).

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The development of acceptable limits and parameters should extend to defining:

- **The aspects of ADME for the compound (adsorption, distribution, metabolism and excretion)**
- **Assuring the target in-vivo profile which is created using simulations and predictions meets the clinical expectations.**
- **The biopharmaceutical classification (BCS) and associated data for the compound have been defined.**
- **Based on the BCS data and the nature of the product functionality what are the risks to determination of bioequivalence and/or the establishment of an IVIVC.**
- **Based on the need for process and site flexibility is the establishment of an IVIVC critical.**

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What risks do you have control over during formulation and process development based on the points we have established?

- **The output for the PAR will be based on tests which we apply (CU, dissolution, assay).**
- **These results can be measured and evaluated.**
- **The nature of the compound while clear from a physicochemical standpoint (solubility) is not as transparent from a drug absorption aspect.**
- **In this regard we must understand that there are points which we can not effect but we must design our process around.**
  - **Low GI permeability**
  - **First pass metabolism**
  - **These are sources of variability to the desired PK profile.**

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How do we gauge this risk aspect in our knowledge store for the product and process?

- **We may define our drug substance by using the BCS categories.**
  - **Class I = high solubility, highly permeability**
  - **Class II = low solubility, high permeability**
  - **Class III = high solubility, low permeability**
  - **Class IV = low solubility, low permeability**
- **These may be further refined by applying additional data to our drug product.**
  - **Absorption number , permeability of the drug substance**
  - **Dose number, the solubility aspect of the drug substance**
  - **Dissolution number, the release from the drug product**

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How do we use this to anticipate PK problems?

Generally the following may be used as a guide:

- **Class I products are usually no problem.**
  - **Assuming we have not created a problem in our process or formulation (secondary growth, blending)**
- **Class II products will usually be no problem**
  - **Assuming we already have comparability in various dissolution media (pH 1, 4.5 , 6.8).**
  - **We have not changed the release mechanism from the tablet due to composition and mixing.**
- **Class III these may be problematic and will require PK studies which are adequately powered (n >12)**
- **Class IV there is no certainty in PK outcomes here one may apply a large n>25 but the use of a small scale pilot study seems advisable.**

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Effort spent in creating an IVIVC relationship early in the development cycle is well placed.

- While not always possible (BCS review) it will yield benefits for formulation and process optimization and the creation of meaningful specifications.
- The data will be specific to the formulation in question which may be considered a downside.

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An IVIVC strategy makes it part of the methods used to guide formulation development. It becomes a part of the knowledge store for the product.

Potential IVIVC Strategy:

- At the product concept phase use a target in vivo profile based on simulations and predictions for an assumed IVIVC.
- The prototype is tested using various dissolution conditions.
- The result will be a comparison of dissolution conditions and methodology with biodata allowing an IVIVC to be established.

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Potential IVIVC Strategy (continued):

- During optimization of the formulation / process the IVIVC is defined and predictions from the IVIVC validated.
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IVIVC Strategy (continued):

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Case Study 1:

Background:

Develop a fixed combination product which will match innovator profiles and form the basis for submission based on bioequivalence strategy.

Objectives:

- Keep tablet size small.
- Protect the two drug substance components from degradation.
- Use available conventional technology.
- Match dissolution profiles for both innovators.

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Case Study 1:

Outcome:

- Tablet size was kept within reasonable range for patient acceptance.
- The in-vitro data provided a reasonable match for both materials under consideration.
- The combination was shown to be stable over 12 weeks at accelerated conditions.
- Move forward with a study to confirm the in-vitro results.

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Case Study 1:

PK Study Results:

- The plasma data showed an increase in the input for the fixed product.
- One of the components showed a marked shift in availability when compared to reference.
- This required a wider approach using various media (pH) and conditions to resolve and enhance the predictive nature of the in-vitro testing.

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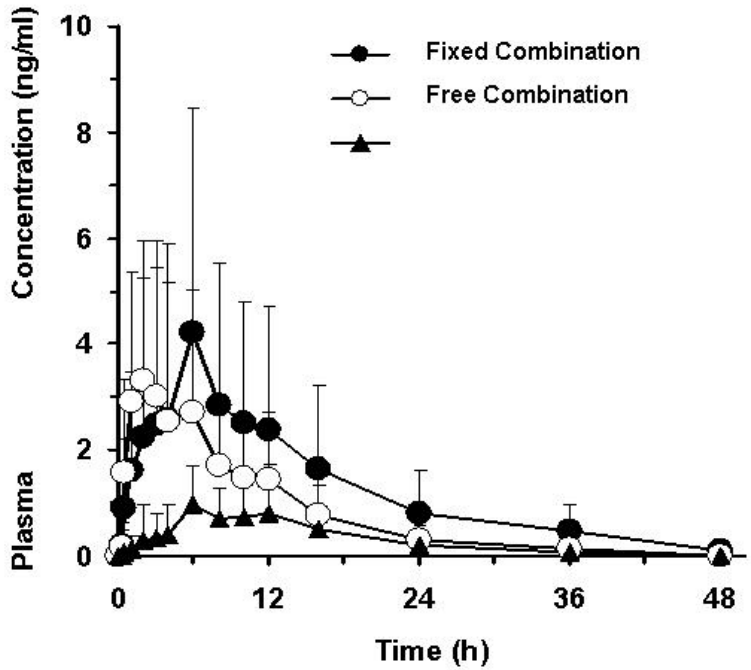

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Case Study 1:

This needed a more critical eye toward some early studies. The knowledge store may have provided some insight.

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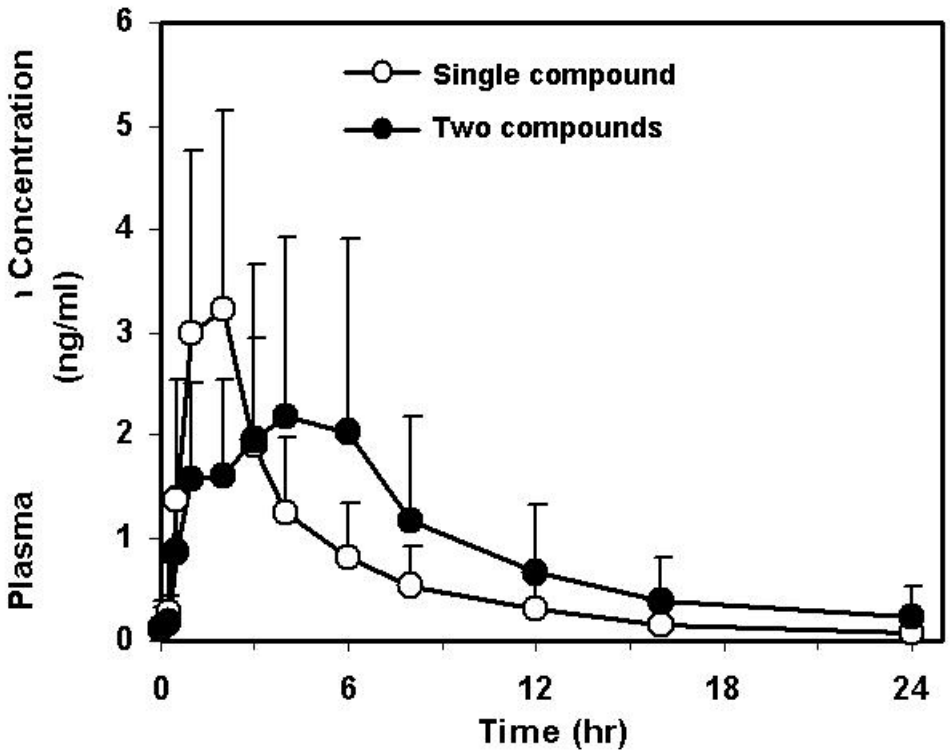

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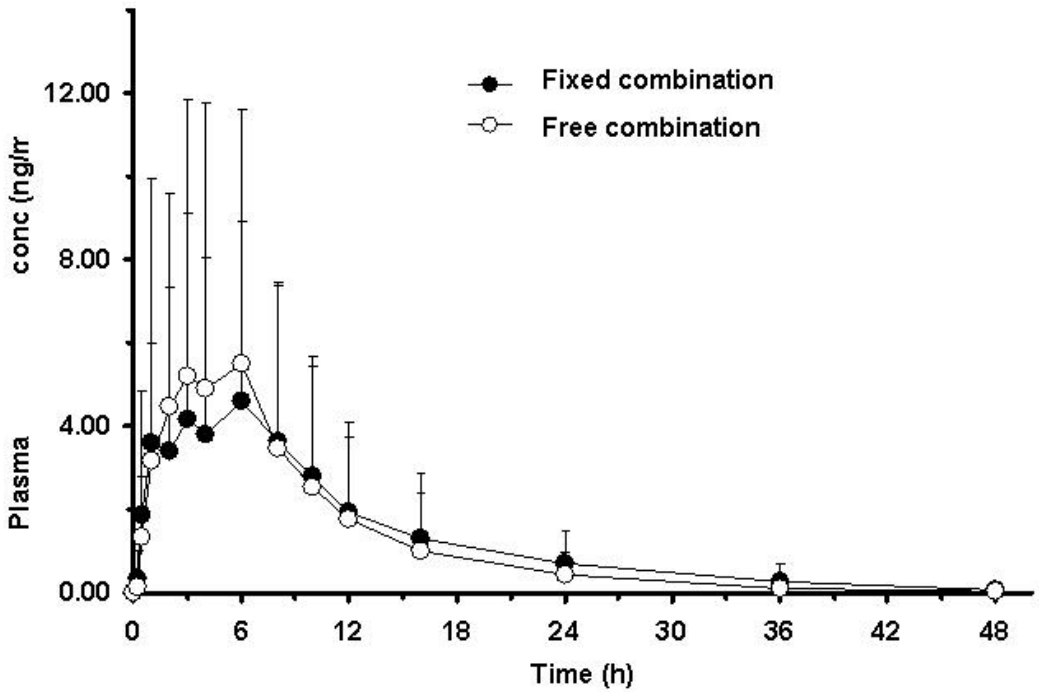

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Case Study 2:

Background:

Develop a modified release product which will match clinical requirements and address an unmet medical need.

Objectives:

- Provide up to 12 hours of activity.
- Maintain dosage form size.
- Use available conventional technology.
- Match current in-vivo profile as established by clinical practice.
- Leverage process and site changes.

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Case Study 2:

Outcome:

- A “fast and slow” study was selected as the best approach to establish a range.
- Clinical materials were prepared based on simulations and the anticipated need for release rate specifications.
- These specifications were balanced against process capability and envisioned variability.
- Move forward with a study to confirm the in-vitro results.

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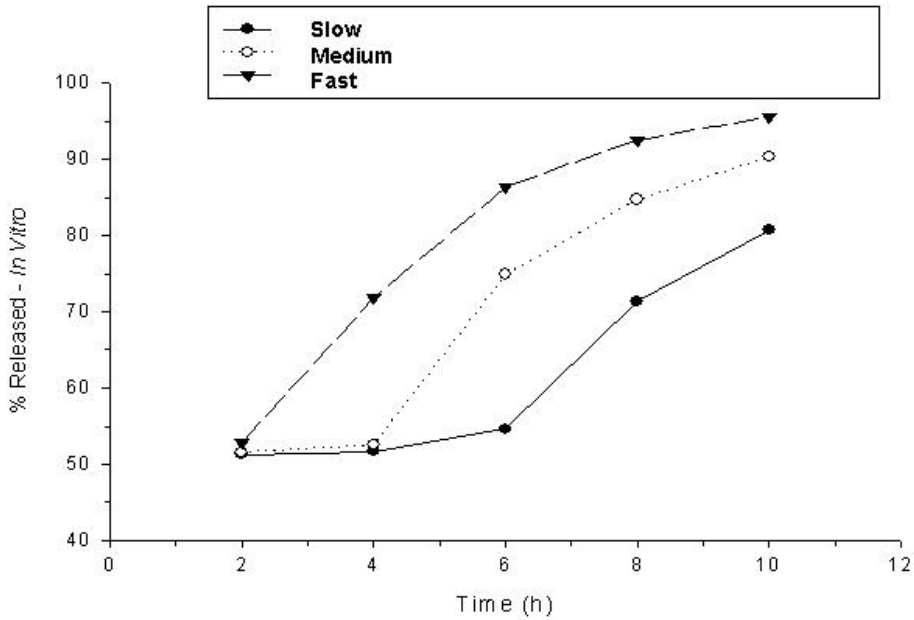

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Case Study 2:

PK Study Results:

- The study was conducted comparing the fast and slow samples to the target as well as a reference.
- This provided the establishment of a BE baseline for the extremes studied in this product.

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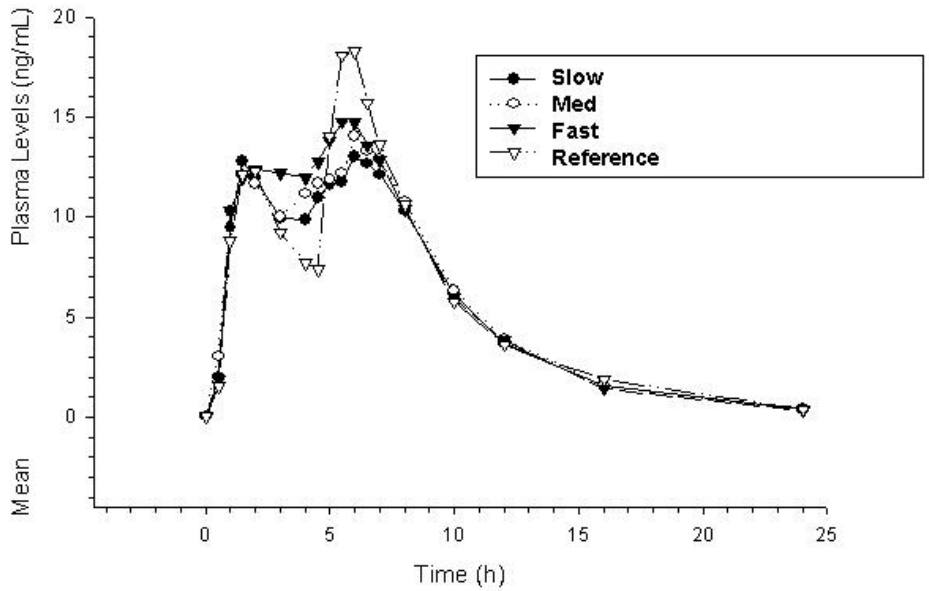

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