



QbD and Applied Biopharmaceutics for Patient Benefit

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Assessment/CDER/FDA**

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Expectations from this meeting

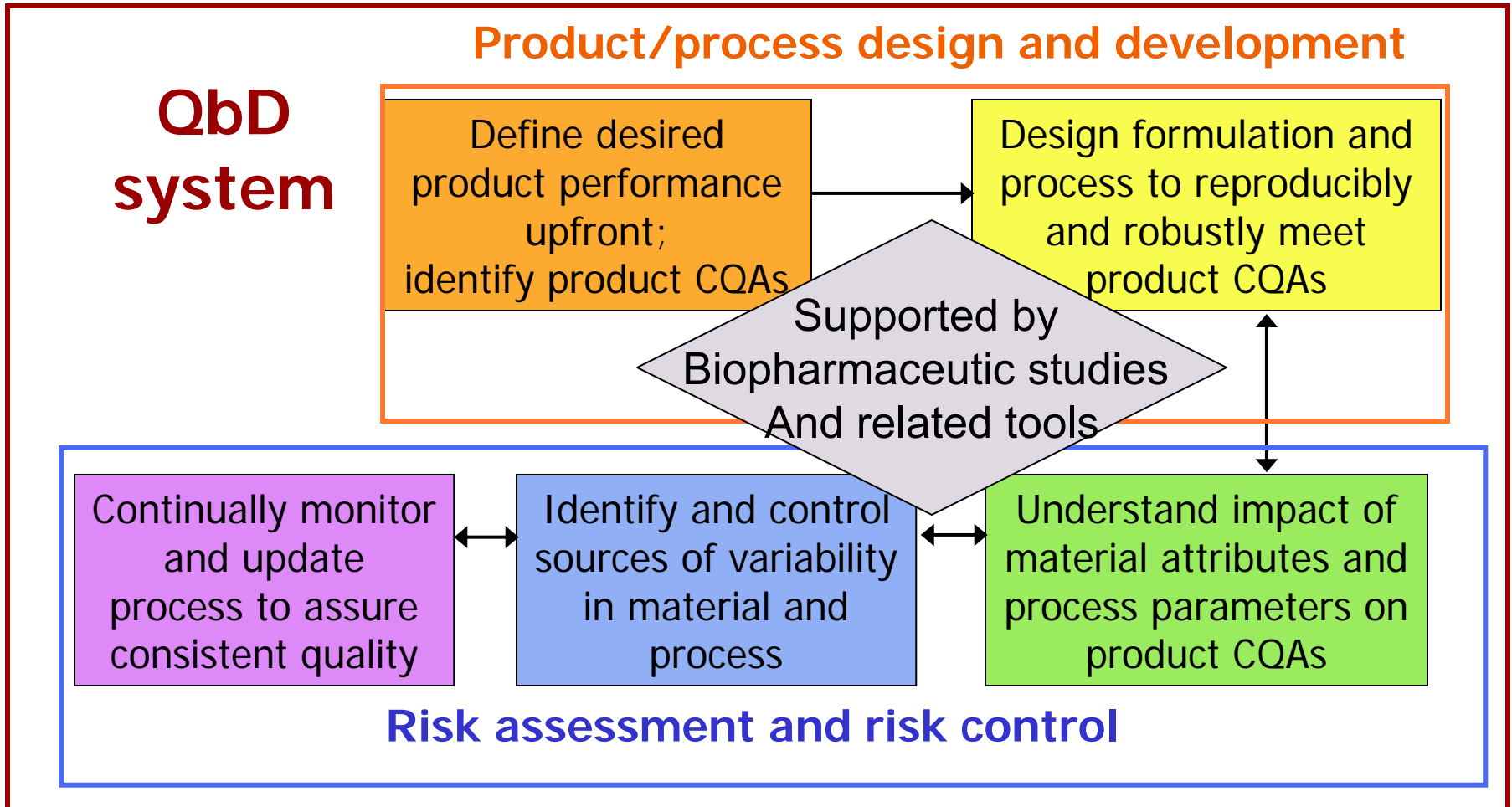
Dialogue on:

- **Integration of QbD and biopharmaceutics for patient benefit**
- **Challenges/opportunities**
 - **Advancing dissolution/drug release testing as a product quality tool**
 - **Predictive methods**
 - **Modeling and simulations**

Outline of My Talk

- **Integrating QbD and Biopharmaceutics (Linking Product and Patient Benefit)**
- **Exploring Opportunities for the patient benefit: Considerations and tools**
- **Summary and What's Ahead?**

Integrating QbD and Biopharmaceuticals



QbD is Product and Process:

- **Product Knowledge** – understanding of how variability impacts product
 - Material variability - PSD, surface area, moisture content, etc.
 - Process variability - granulation, tableting conditions, etc.
- **Product Specification** – to provide continued assurance of clinical performance
- **Product Performance**
 - ensuring product quality as dissolution links/relates product attributes to clinical performance

The Three Considerations Critical for Quality (Patient Benefit):

Product:

- Designed to meet intended use
- Consistently delivers the desired/intended dose

Manufacturing Process:

- Designed to consistently meet product critical quality attributes
- Suitable for continuous monitoring and updates and allows for consistent quality over time (life cycle)

Understanding the Main Sources of Variability:

- Due to starting materials and process
- Due to Methodology and assumptions
- Due to product-patient interface and the patient

A Path to Integrating QbD and Biopharmaceutics:

- Determine/estimate key product characteristics (**target product profile**)
- Develop and verify **in vitro methods** such as drug release/dissolution method and characteristics against target product profile **and in vivo** data
- Identify the **relationship** between product attributes and in vivo performance
- Determine the sources of **variability** and factors that need to be modified to optimize the product
- **Build on knowledge** gained to optimize the product (iterative process)

Considerations and Tools

Building Blocks: In vitro studies

- What in vitro characteristics will achieve in vivo target?
- What is the clinical relevance of in vitro methods?
 - Is in vitro data (model) predictive of in vivo performance?
- What is a **significant** change in in vitro dissolution/release?
- How can in vitro dissolution/release be altered to achieve in vivo target?

Building Blocks (continued)

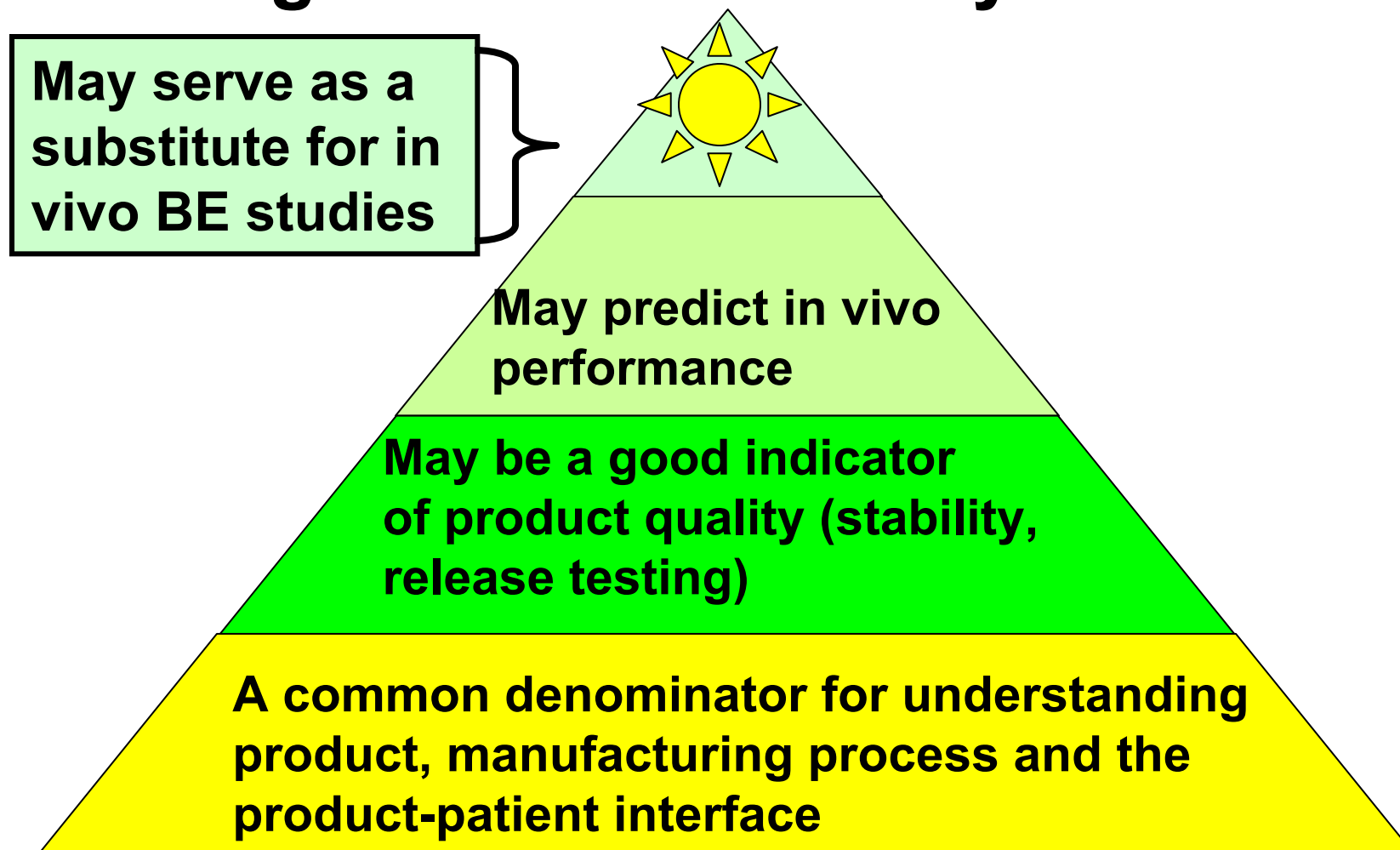
In vivo studies:

- Is study design suitable to address the question e.g.
 - exploring product performance in relation to design space for a specific drug product
 - prototype selection
 - formulation optimization
 - for method optimization (extrapolating from animal studies)

In silico studies:

- Can in vitro and in vivo data be utilized for model development? (Driven by study purpose and supporting data)

In vitro Dissolution/Release Testing: A Product Quality Tool



IVIVC or IVIVR: Quality Tool and More

- Based on **established IVIVC**
 - in vitro dissolution data serve as a surrogate for human BE studies
 - in vitro dissolution specification has in vivo relevance
 - guides product development by predicting in vivo performance
- **Optimized/Advanced IVIVC/IVIVR** testing may bridge routine testing results (such as those at product release) to in vivo product performance.

Other Considerations/Opportunities:

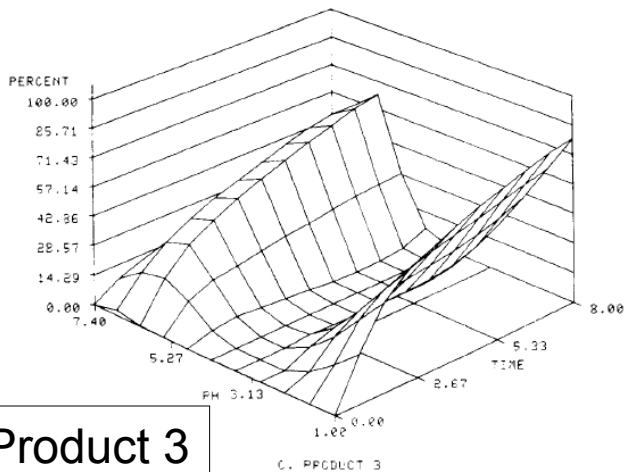
- **disintegration or some other quality attribute may be a substitute for in vitro dissolution**

As long as quality performance of drug products may be assured throughout their intended shelf-life.

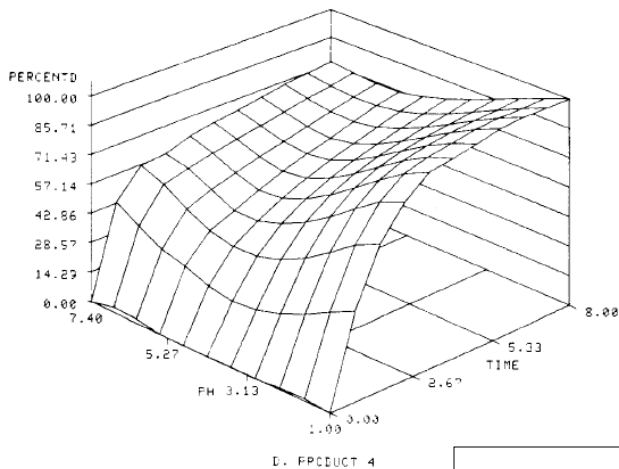


A Corner Stone and 3 Examples

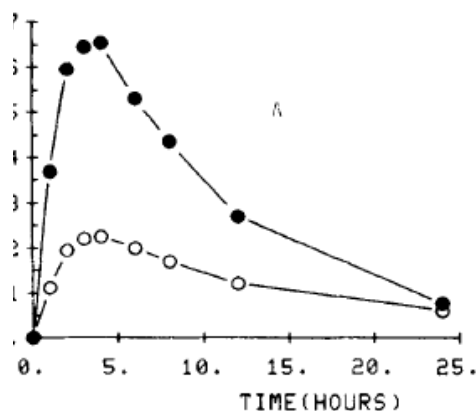
One of the Early Corner Stones: Similar dissolution at pH 1



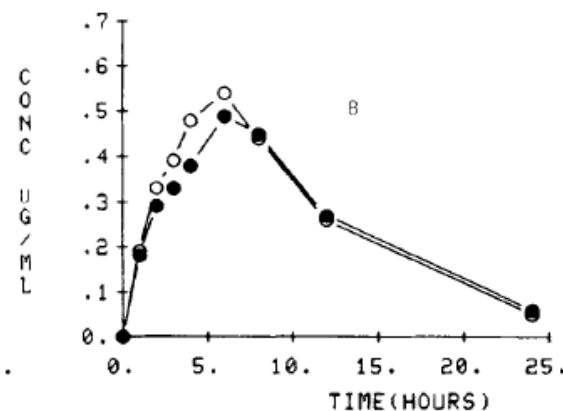
Product 3



Product 4



-○- PRODUCT3
-●- PRODUCT1



-○- PRODUCT4
-●- PRODUCT1

Figure 1

J.P. Skelly, M.K. Yau, J.S. Elkins, L.A. Yamamoto, V.P. Shah and W.H. Barr. In vitro topographical characterization as a predictor of in vivo controlled release quinidine gluconate bioavailability. Drug Dev. Indust. Pharm. 12(8&()), 1177-1201, 1986

Example 1: Response Surface Approach (Developing A Story for Drug X)

Objective:

Preparing a drug delivery system for Drug X

Methods:

- Nine prototypes were developed
- Full 3^2 factorial design was applied to optimize drug release profile and for determining the composition of key excipients
- Selection criteria: highest in similarity to the theoretical/desired dissolution profile using $t_{50\%}$ (time 50% dissolved) and $t_{80\%}$ (time 80% dissolved)

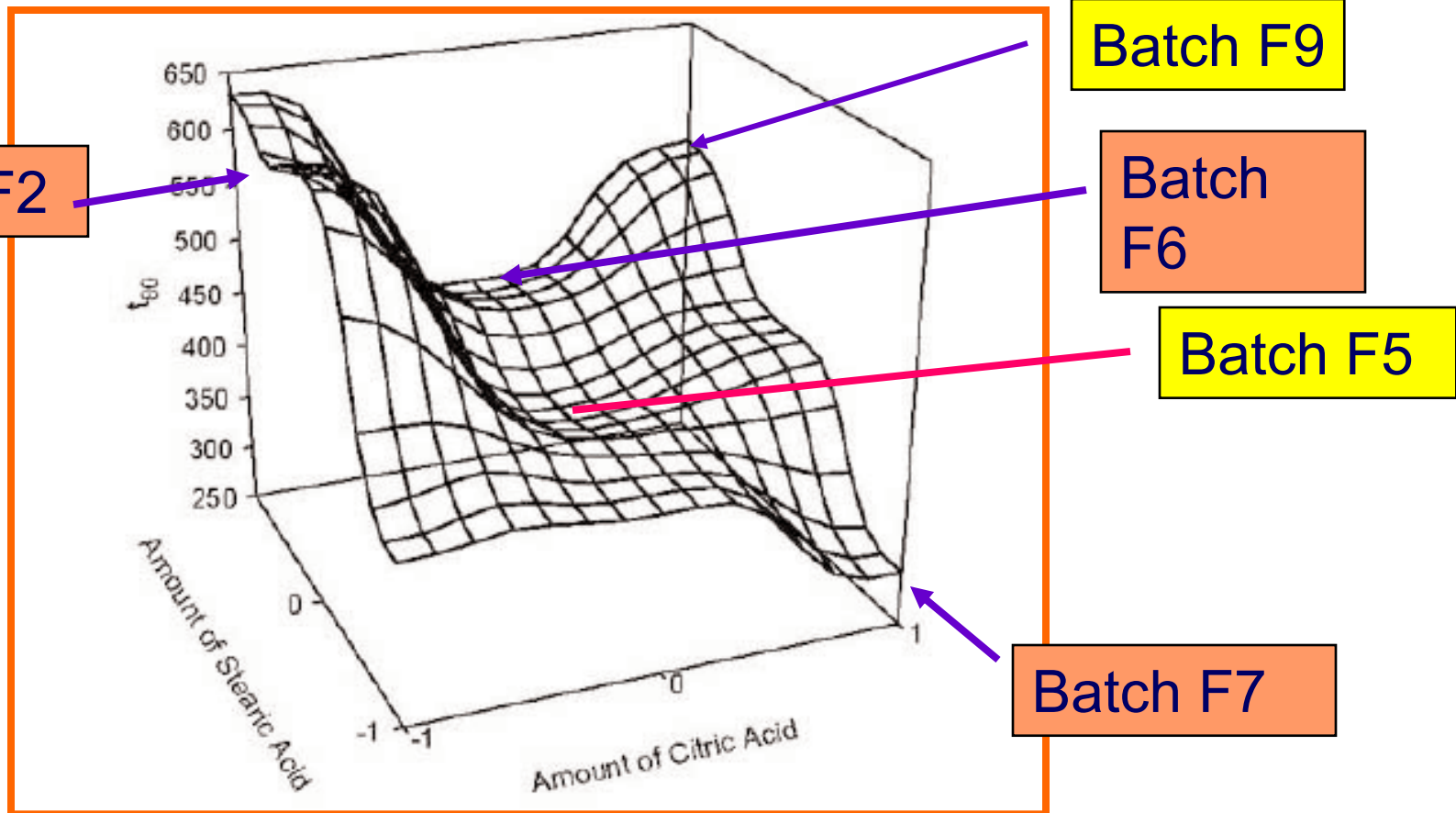
Results:

Table 2. Formulation and Dissolution Characteristics of Batches in a 3² Full Factorial Design*

Batch Code	Variable Level in Coded Form [†]		t ₅₀ (minutes) ± SD	t ₈₀ (minutes) ± SD	Similarity Factor f2
	X ₁	X ₂			
F1	-1	-1	86 ± 1.2	392 ± 3.1	45
F2	-1	0	139 ± 1.8	625 ± 4.6	52
F3	-1	1	190 ± 2.3	631 ± 2.5	52
F4	0	-1	79 ± 0.8	392 ± 5.1	45
F5	0	0	121 ± 2.3	391 ± 4.6	46
F6	0	1	160 ± 2.1	429 ± 1.6	51
F7	1	-1	38 ± 0.7	297 ± 4.9	37
F8	1	0	96 ± 2.6	431 ± 6.4	47
F9	1	1	214 ± 0.8	537 ± 5.9	75
Theoretical			221	523	-

Coded values	Actual values [†]	
	X ₁	X ₂
-1	0	0
0	5	5
1	10	15

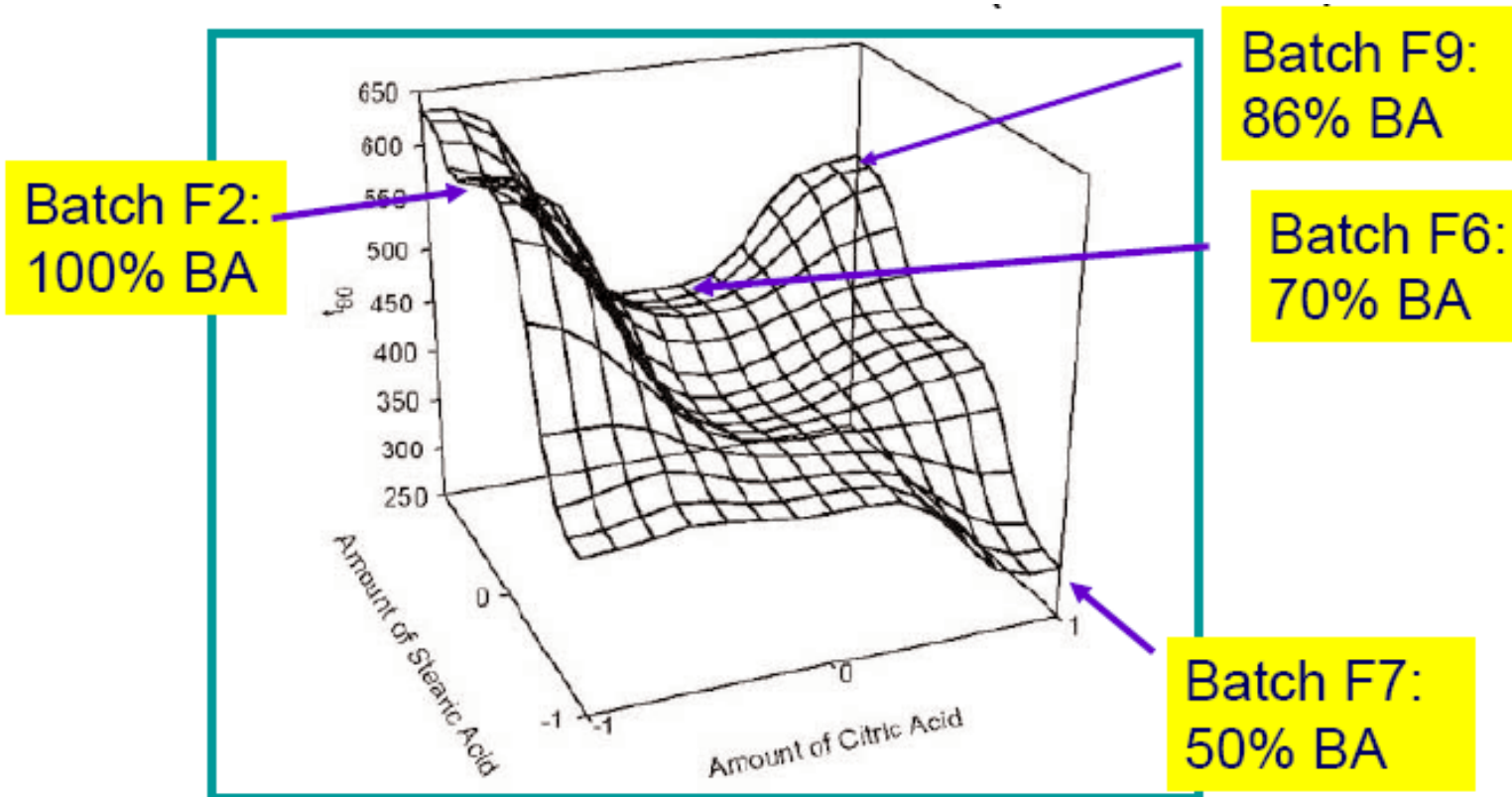
Batches of Drug Product X and Time for 80% dissolved (seconds)



Assumptions to Build a Story:

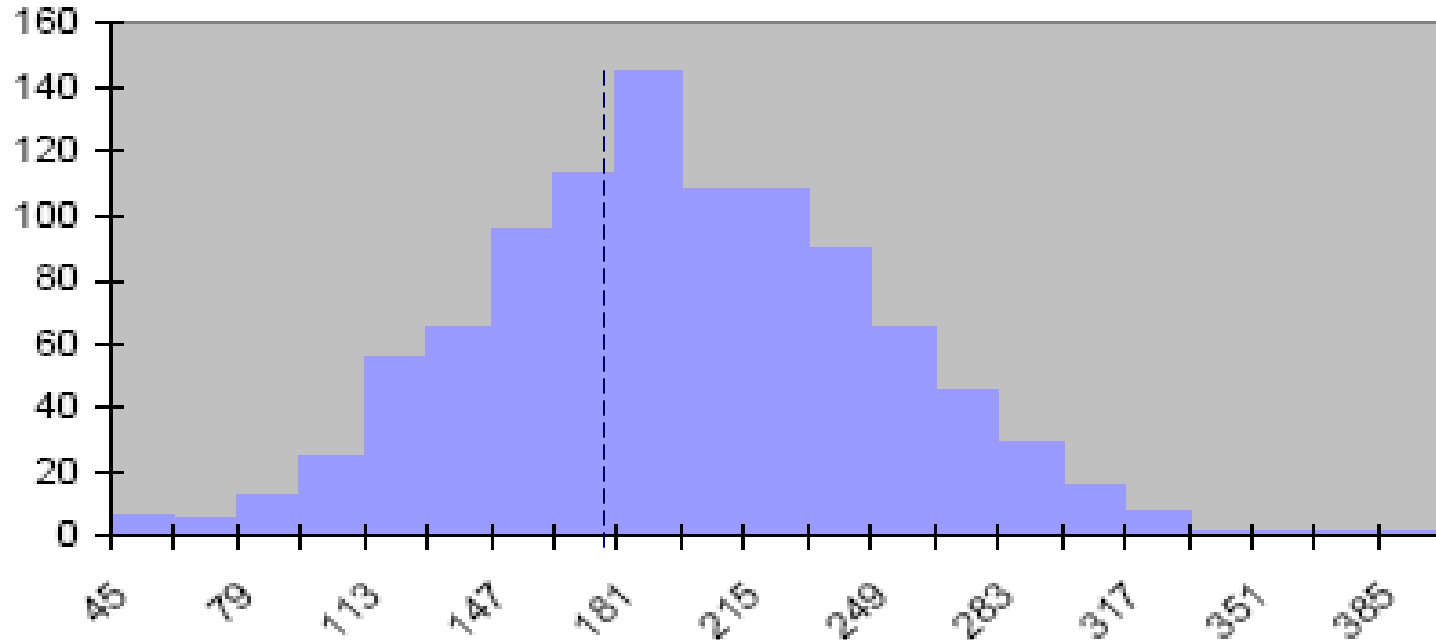
- AUC(0-6h) values predict clinical outcome
- T80% response surface maps directly to AUC(0-6h)
- **For clinical efficacy: $AUC(0-6h) \geq 150 \text{ ng.h/mL}$**
- AUC values follow normal distribution
- Variances are additive
- CV% of 5% in T80% is representative of all product related variability in our example
- Based on a literature publication for Drug X:
mean(CV%) for AUC(0-6h) is 180 ng.h/mL (30%)

Continuing with the Story: Batches of Drug Product X and time for 80% dissolved



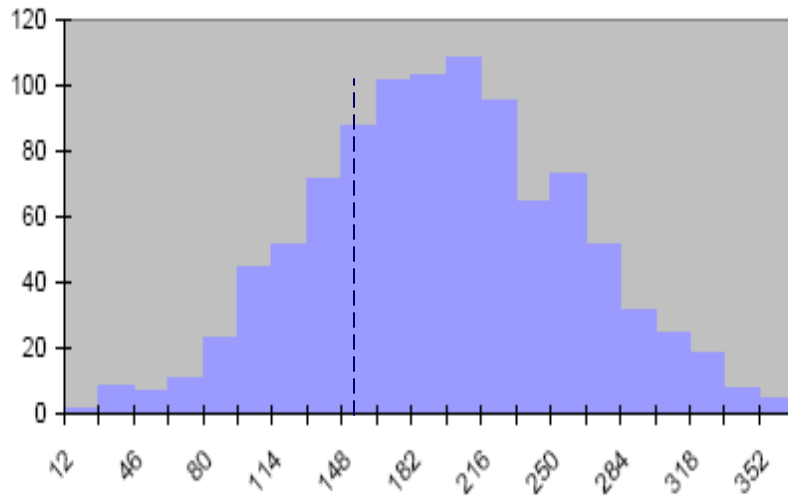
What percent of patients will have a favorable clinical outcome if they take these batches of Drug X?

Simulation: Histogram (Drug X, Dose:A, typical mean AUC(0-6): 180 ng.h/mL, CV% 30%)



Simulation: n=1000 based on “typical” (literature) data, approximately 75% of the patients will have target AUC(0-6h) values

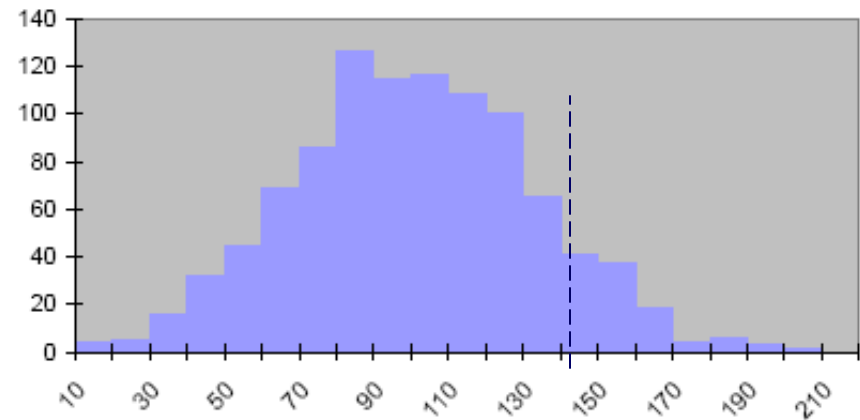
Simulation: Histogram, Batch F2 (same dose, same BA, CV%:35%)



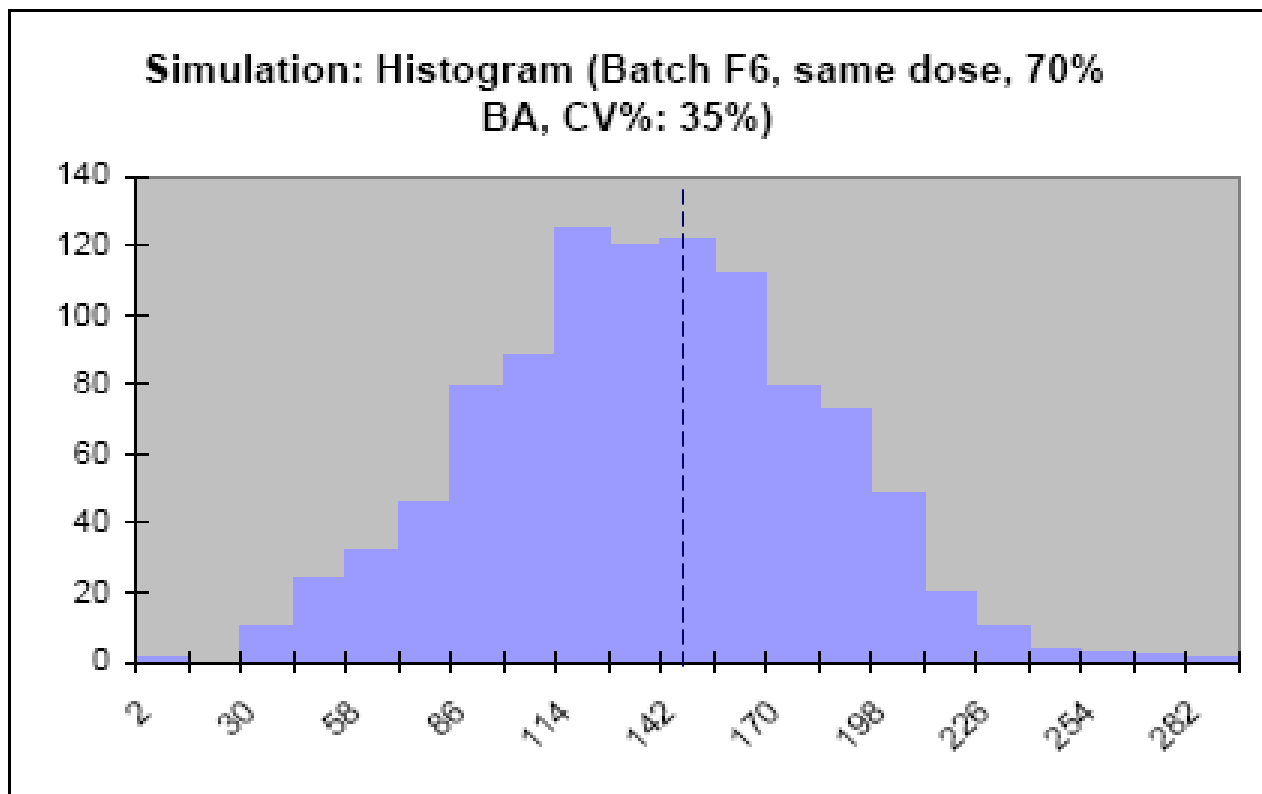
Batch F2: Approximately 70% of patients will have AUC(0-6h) values ≥ 150 ng.h/mL

Batch F7: Approx. 7% of patients will have AUC (0-6h) values ≥ 150 ng.h/mL

Simulation: Histogram (Batch F7, same dose, 50% BA, CV%:35%)



A possible choice: Batch F6?



Approximately 40% of the patients will have AUC(0-6h) values ≥ 150 ng.h/mL

Summary of simulation results:

Drug Product X (Bioavailability)	Mean (CV%) AUC(0-6) (ng.h/mL)	Percentage of Patients likely to benefit (i.e. AUC(0-6) \geq 150 ng.h/mL)
Literature (100%)	180 (30%)	Approx. 75%
Batch F2 (100%)	180 (35%)	Approx. 70%
Batch F9 (86%)	155 (35%)	Approx. 60%
Batch F6 (70%)	126 (35%)	Approx. 40%
Batch F7 (50%)	90 (35%)	Approx. 7%

Moving Forward with Drug X?

Things we know/estimated:

- Effect of varying excipient content on in vitro dissolution
- Relationship between dissolution and estimate of clinical outcome (target AUC(0-6h) values)
- Possible/potential in vivo outcomes, based on simulations, for the prototypes

Need to explore

- Verify “**stable**” regions on the response surface
- **Identify parameters which may be optimized** to achieve desired clinical outcome in a greater percentage of patients.
- Identify sources of variability and evaluate their potential effect on “promising” candidate(s)

Evaluate and further refine the prototype(s) likely to be of clinical benefit in a “suitable” PK study.

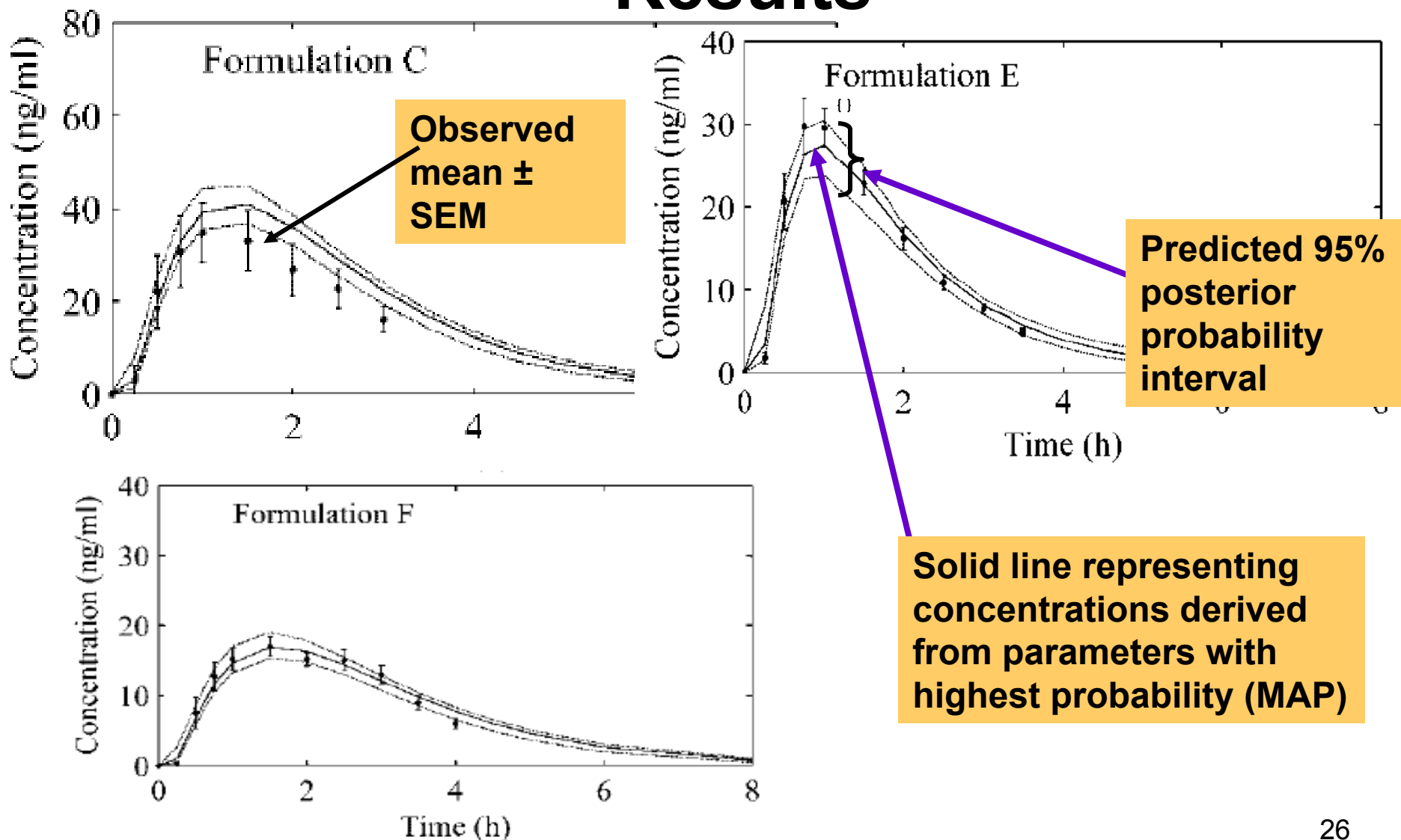
Example 2: Incorporating “variability” to optimize IVIVC modeling

Objective: Develop an IVIVC model that provides predictions with probabilities

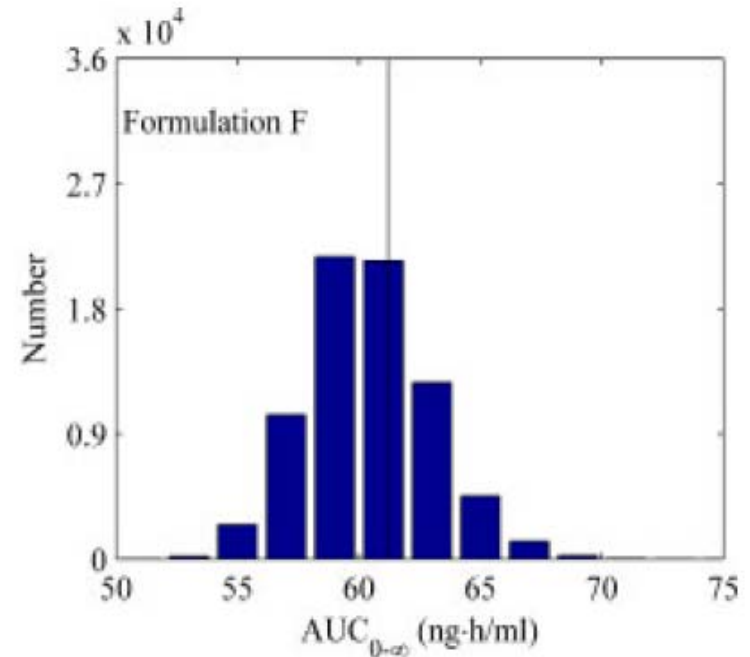
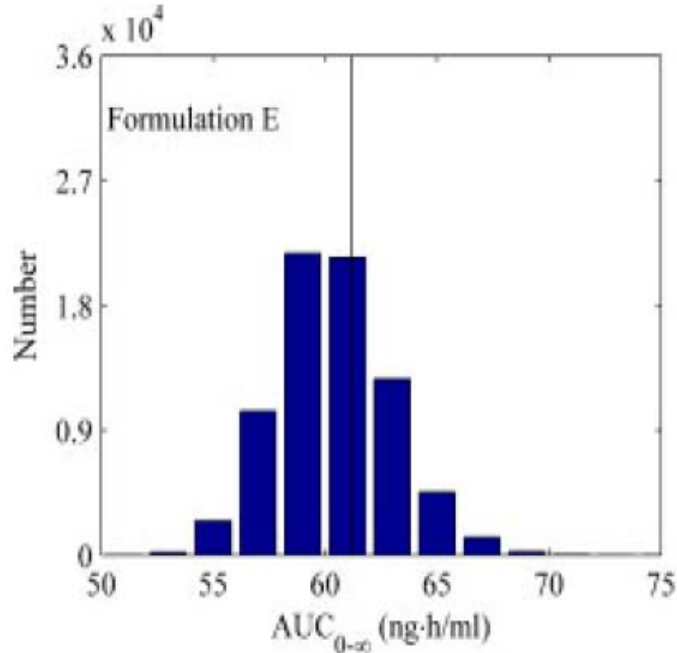
Approach: Uncertainty related to model and data were incorporated by Bayesian approach, enabling prediction of plasma concentrations with probability distributions.

H. Kortejärvi, J. Malkki, M. Marvola, A. Urtti, M. Yliperttula, P. Pajunen, J. Pharm. Sci. 95, #7, pages 1595-1605, 2006

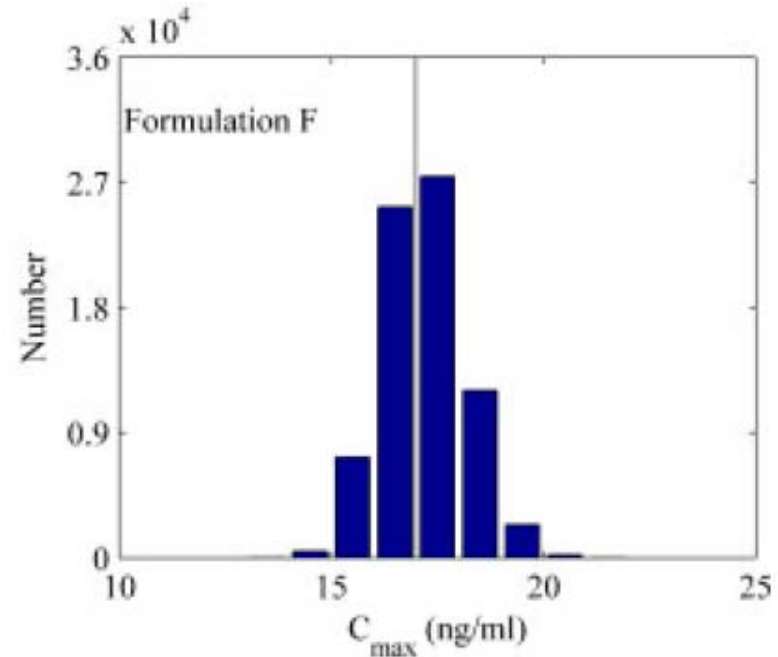
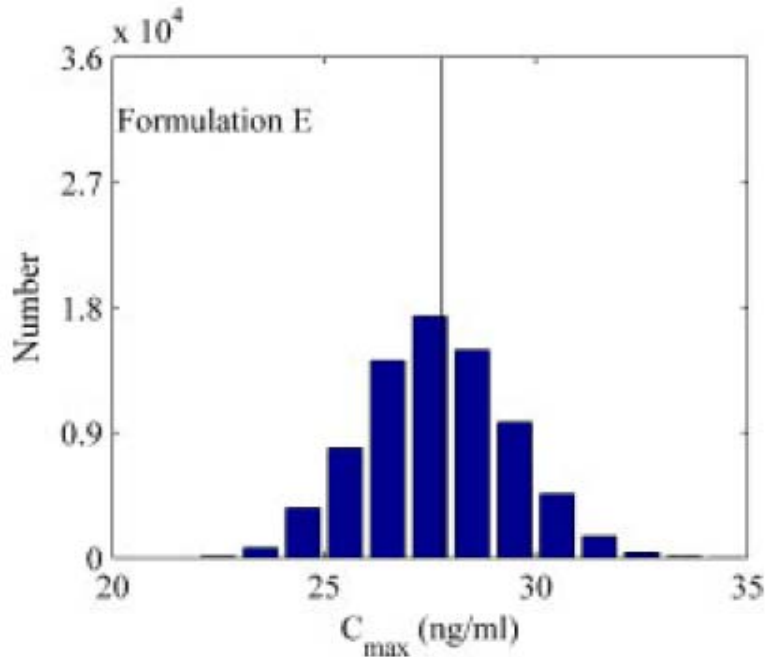
Results



Parameter distributions predicted with dissolution data and posterior distribution of model PK parameters



Parameter distributions predicted with dissolution data and posterior distribution of model PK parameters



Highlights of Example 2

- Incorporates **variability** and predicts concentration-time profiles and PK parameters as probability distributions
- **Builds uncertainty into the IVIVC model**
- Provides an **information rich IVIVC** assessment with a likely range of in vivo data/parameters

Example 3: *in silico* Modeling And Simulation

Goal: To determine optimal *in vivo* delivery rate for efficacy

Approach:

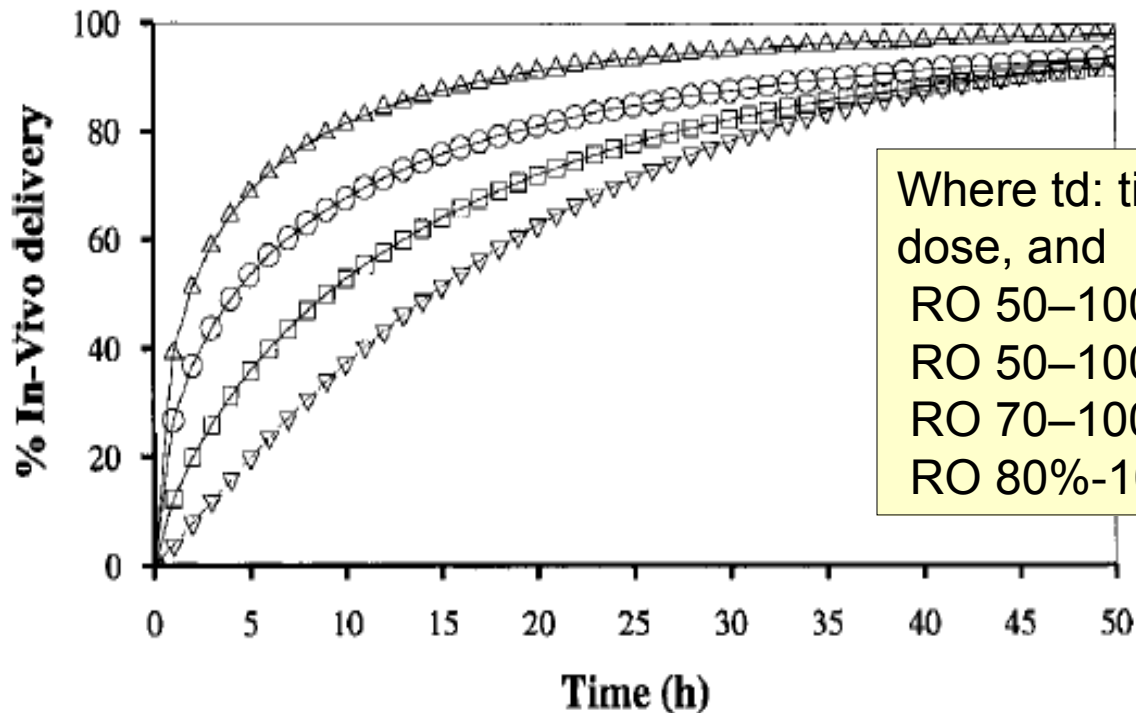
- Used receptor occupancy (RO) data from PET studies, EC50 estimates from *in vitro* binding studies
- Feedback control to identify the optimal *in vivo* delivery rate (from same class compounds)
- Explored inter-individual variability ranging from 10% to 30% on absorption, disposition and potency

R. Gomeni, C. D'Angeli, and A. Bye. "*In Silico* Prediction of Optimal *in Vivo* Delivery Properties Using Convolution-Based Model and Clinical Trial Simulation" *Pharm. Res.* Vol. 19 (1), 99 -103, 2002.

Simulation of in vivo delivery:

Based on Weibull model and adaptive feedback control algorithm as a function of the targeted therapeutic window.

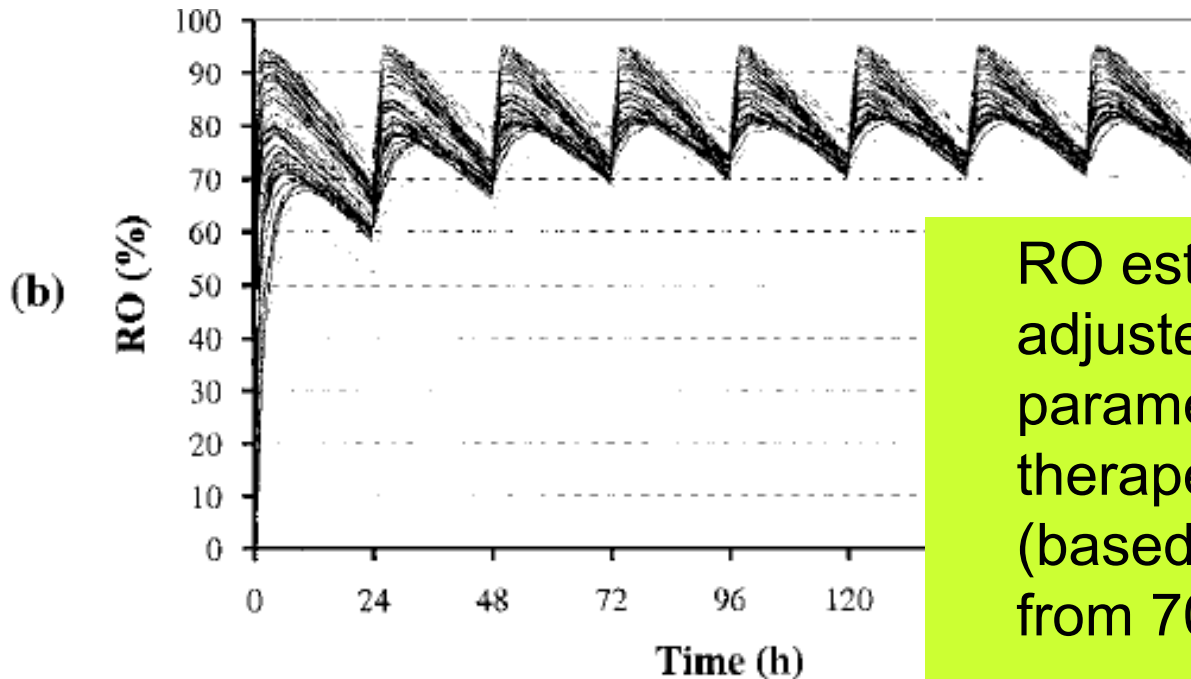
In Silico Prediction



Where t_d : time for delivery of 63.2% of dose, and β : shape factor
 RO 50–100%, t_d 3.75, β 0.53 (Δ);
 RO 50–100%, t_d 8.08, β 0.56 (\circ);
 RO 70–100%, t_d 14.6, β 0.76 (\square) and
 RO 80%-100%, t_d 20.3, β 1.08 (\blacktriangleright).

Prediction:

Time-course of the individual (n=100) RO values after administration of 30-mg oral dose, once a day for a week



RO estimated with the adjusted *in vivo* delivery parameters and a therapeutic window (based on RO) ranging from 70% to 100%.

Highlights of Example 3

- Utilized predictive mathematical modeling to assess the relationship between the *in vitro* dissolution/release and *in vivo* response time course
- Explored the relationship between “desired” clinical outcome, and *in vitro* dissolution/release characteristics in the presence of uncertainty from multiple sources.

Summary and What's Ahead?

- Effective integration of QbD and biopharmaceutics is leading to innovative approaches linking the product/process knowledge and understanding to patient benefit.
- We are poised for advances in application of IVIVC/R for patient benefit using current/advanced/borrowed tools and need to continue exploring possibilities.
- Collaboration and innovation will define our path for moving forward to science and risk-based balanced approaches for ensuring patient health benefit.

Acknowledgements

- Moheb Nasr, Ph.D.
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