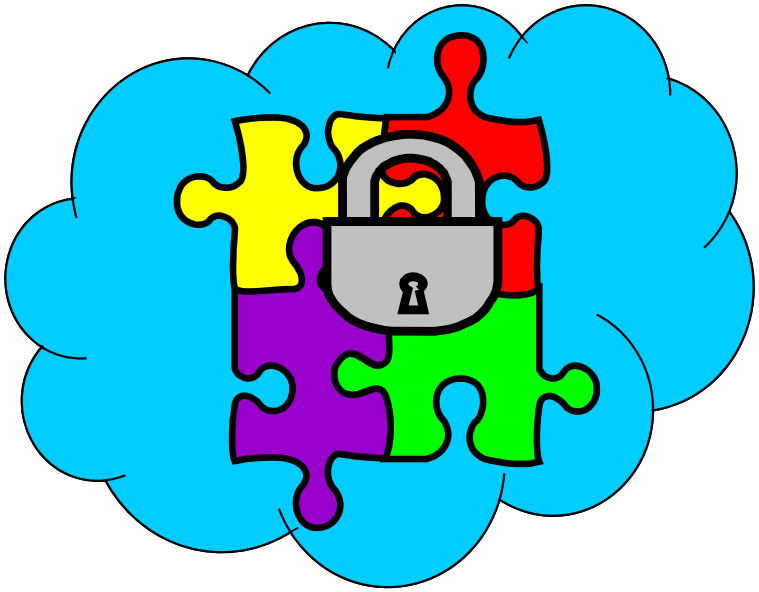
Dissolution Testing and Isothermal Microcalorimetry in QbD



Outline

- Quality by Design
- Product lifecycle
- Biowaivers
- Process knowledge
- Predictive Model
- Conclusions

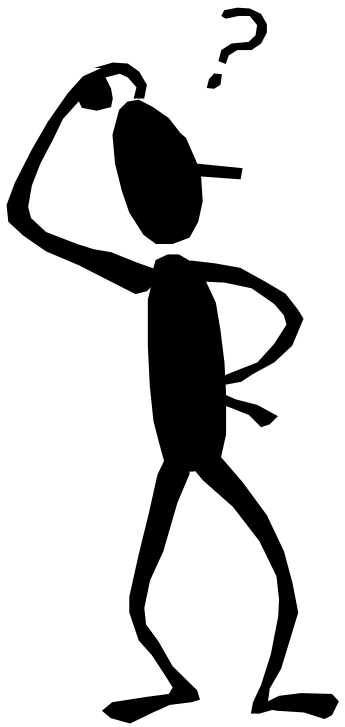
Quality by Design

Product Quality Implementation Lifecycle Initiative (PQLI)

- **Quality by Design** is a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding based on sound science and quality risk management.
  - ICH Q8 Pharmaceutical Development
  - ICH Q9 Quality Risk Management
  - ICH Q10 Quality Systems
  - FDA Pharmaceutical cGMPs for the 21st Century - A Risk-Based Approach. Final Report

Design Space: ICH Q8

- Multi-dimensional space that encompasses combinations of product design, manufacturing process design, manufacturing process parameters and raw material quality that provide assurance of suitable quality and performance

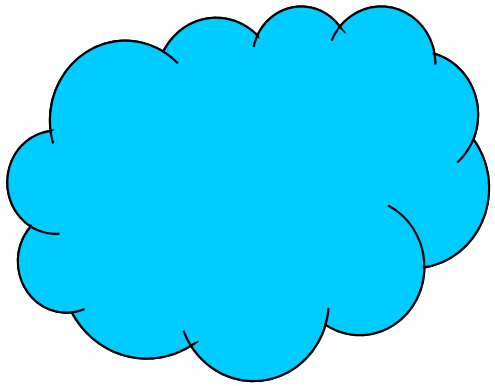


Key Elements of QbD

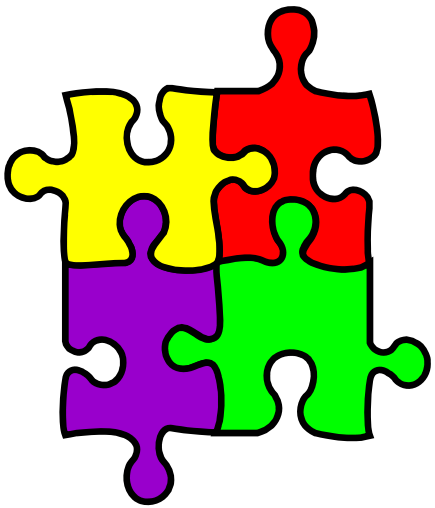
- Define design space
  - Properties
- Risk assessment
  - Critical vs. Non-Critical Parmeters
- Control strategy
  - Key raw material and excipient properties
  - Key processing parameters
    - Set points
    - Processing times
  - Process Analytical Technology (PAT)
  - Product testing requirements.

Design Space (PQLI)

- Integration of prior knowledge



- Creation of a design space is to develop sufficient process understanding to describe the functional relationships between Process Parameters and Critical Quality Attributes.



Design Space (PQLI)

- The functional relationships between Process Parameters and CQAs are best described with a predictive model based upon sound scientific principles, simulations, or experimentation.

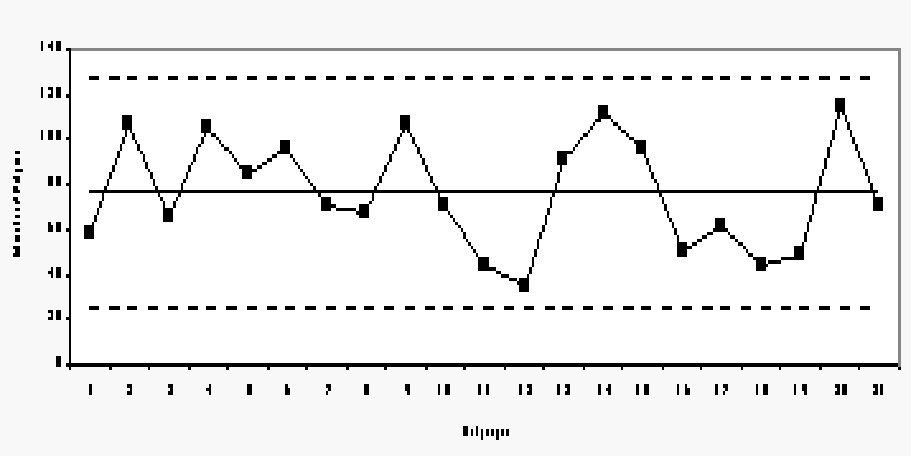
A Process is well understood when…

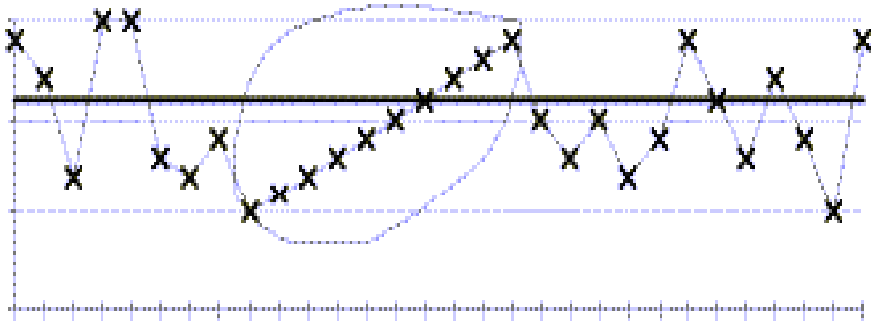
- All critical sources of variability are identified and explained;
- Variability is managed by the process; and,
- Product quality attributes can be accurately and reliably predicted over the design space
- An ability of continuous improvements
- "Real Time" assurance of quality

CONTROL SPACE

Evaluating Variability

- Utilize Process capability analysis – reduce/control "common cause" variability
- Develop effective Corrective Action and Preventive Action will eliminate "special cause" variability





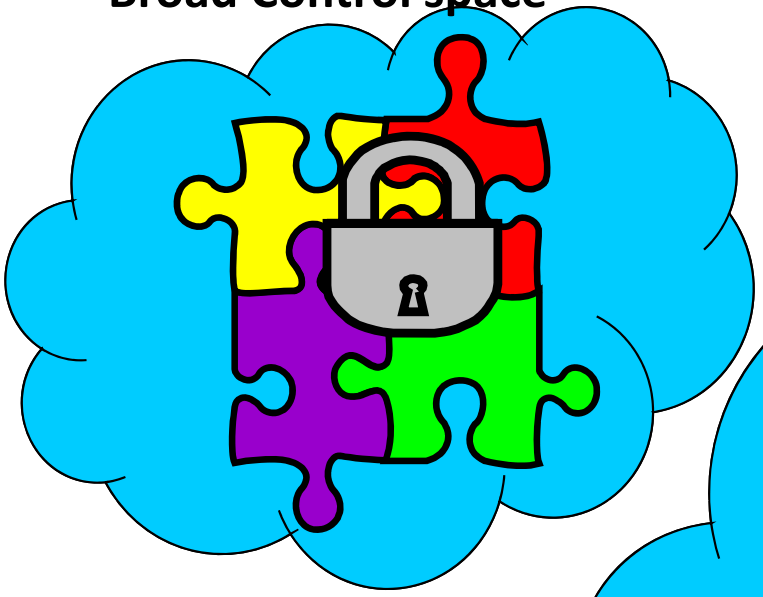
Risk Assessment in QbD

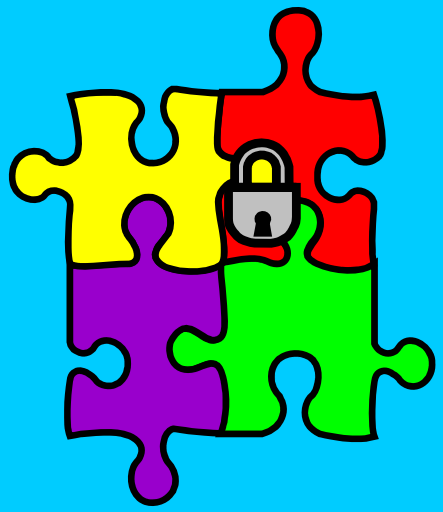
- Probability – the likelihood of a consequence.
- Severity – the magnitude of the impact of a consequence.
- Detectability – the level or ability at which a consequence can be measured.
- Sensitivity – the attenuation of interactions between multivariate dimensions.

QbD & Lifecycle

Start of the project

- **Limited Knowledge**
- **Defined Designed space**
- **Broad Control space**





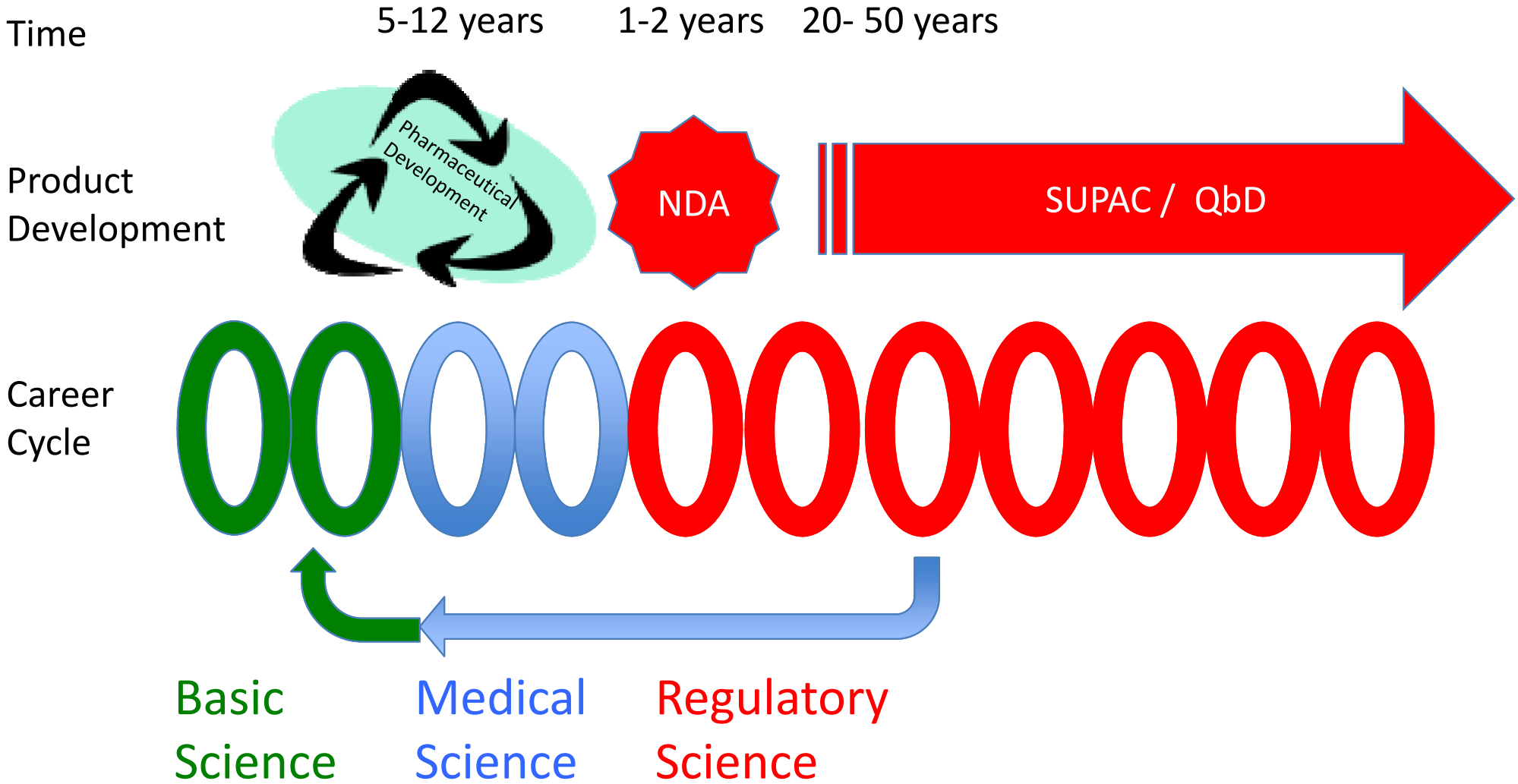
End of the Lifecycle

- **Large Knowledge**
- **Same Design Space**
- **Narrow Control space**

The Six Things to Remember

- We know….
- We want to know…
- We learned …..
- We control …….
- We understand, agree & approve & revise
- We monitor and release!!!

Product Lifecycle Challenge

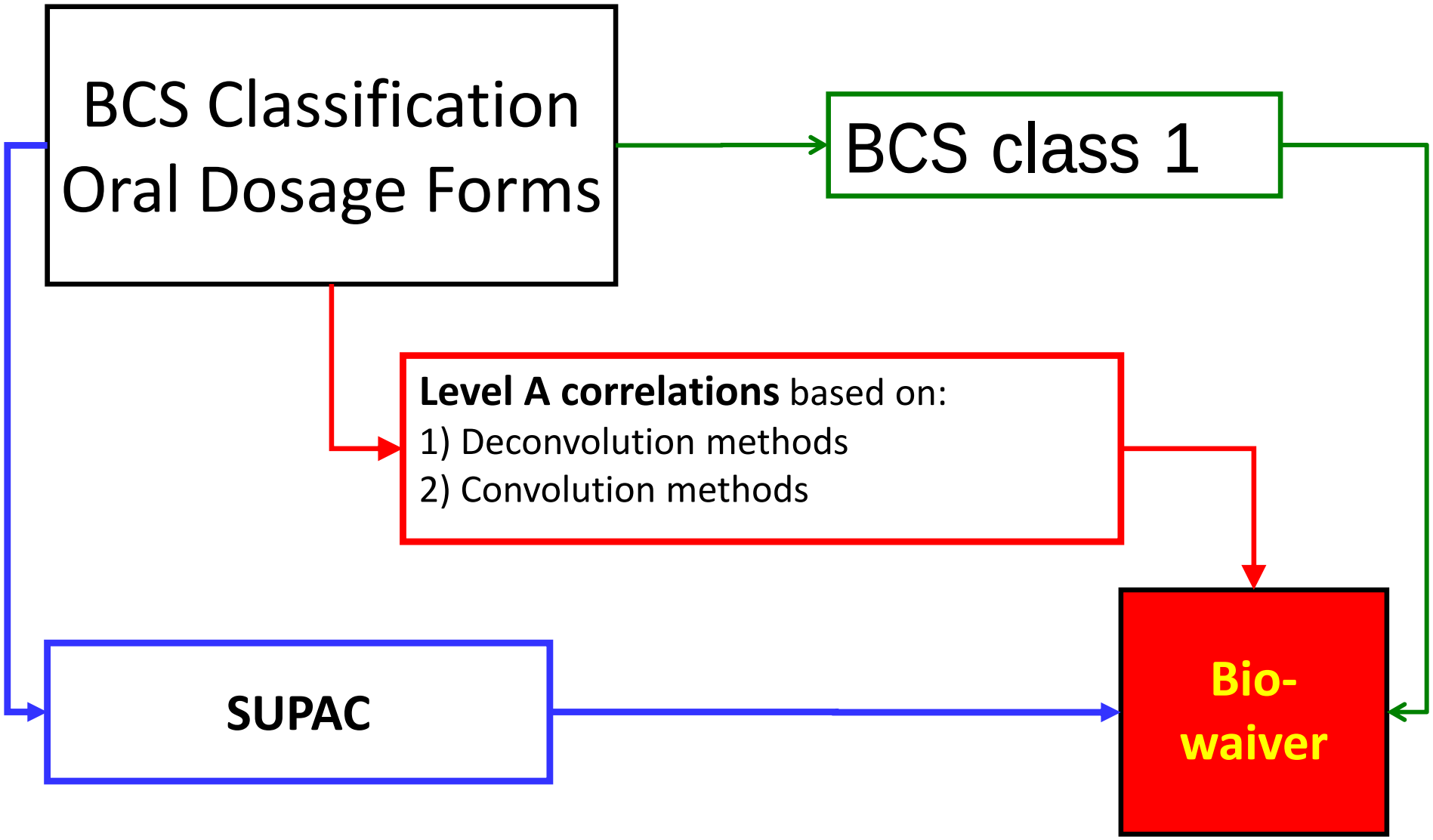


Regulatory Lifecycle of a Product

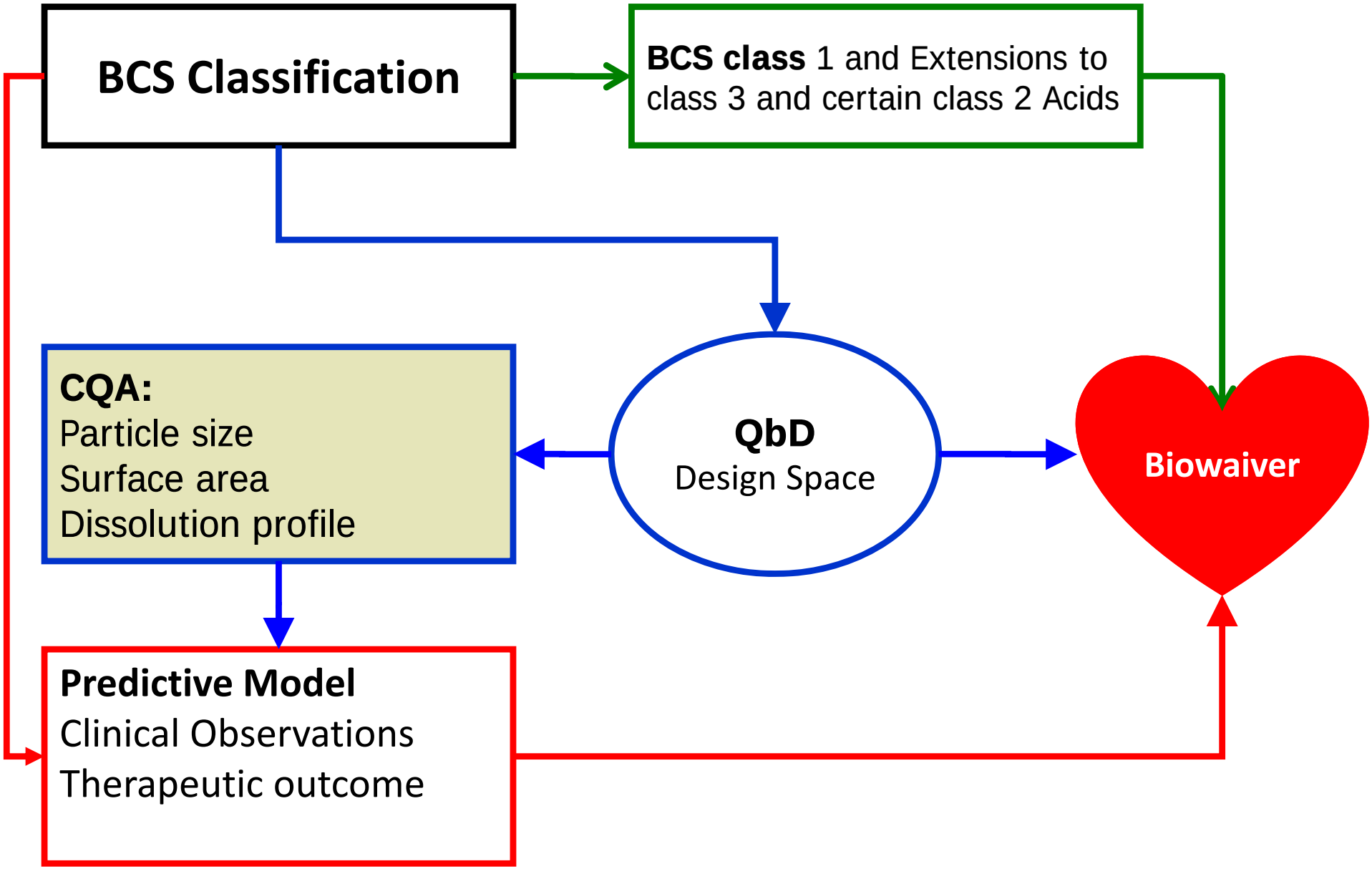
What do I have to do when a change is necessary?

- SUPAC 1995
  - ingredients, equipment – dissolution test as surrogate
  - Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation
- IVIVC 1997 ER
  - Modeling and dissolution as surrogate using a level A correlation
  - Extended Release Oral Dosage Forms: Development, Evaluation, and Application of In Vitro/In Vivo Correlations
- Biowaiver 2000
  - Drug classification as surrogate
  - Waiver of in vivo bio-equivalence studies for immediate release solid oral dosage forms containing certain active moieties/active ingredients based on a Biopharmaceutics Classification System"

Biowaiver Today



Biowaiver Tomorrow



Example for an predictive model

In vitro/in vivo Correlation

USP: *"the establishment of a* ***rational relationship*** *between a biological property, or a parameter derived from a biological property produced by a dosage form, and a physicochemical property of characteristic of the same dosage form" (USP 29)*

FDA defines IVIVC as *"A* ***predictive mathematical model*** *describing the* ***relationship*** *between an in vitro property of a dosage form (usually the rate and extent of drug dissolution or release) and a relevant in vivo response, e.g., plasma drug concentration or amount of drug absorbed" (FDA September 1997)*

Deconvolution-based IVIVC methods

- These methods are **two-stage** modeling procedures

- In the first stage, a deconvolution method is used to estimate the time course of in-vivo absorption (fraction absorbed f_{abs} vs. time t).
- In the second stage, the in-vivo absorption (or release) time profile obtained in this first stage is plotted vs. the time course of the in-vitro dissolution profile.
- Usually a point-to-point relationship is established between the in-vivo and in-vitro parameters of the same time point (e.g., in-vivo fraction absorbed f_{abs} vs in-vitro fraction dissolved f_{dis});
- Linear or sigmoidal curves

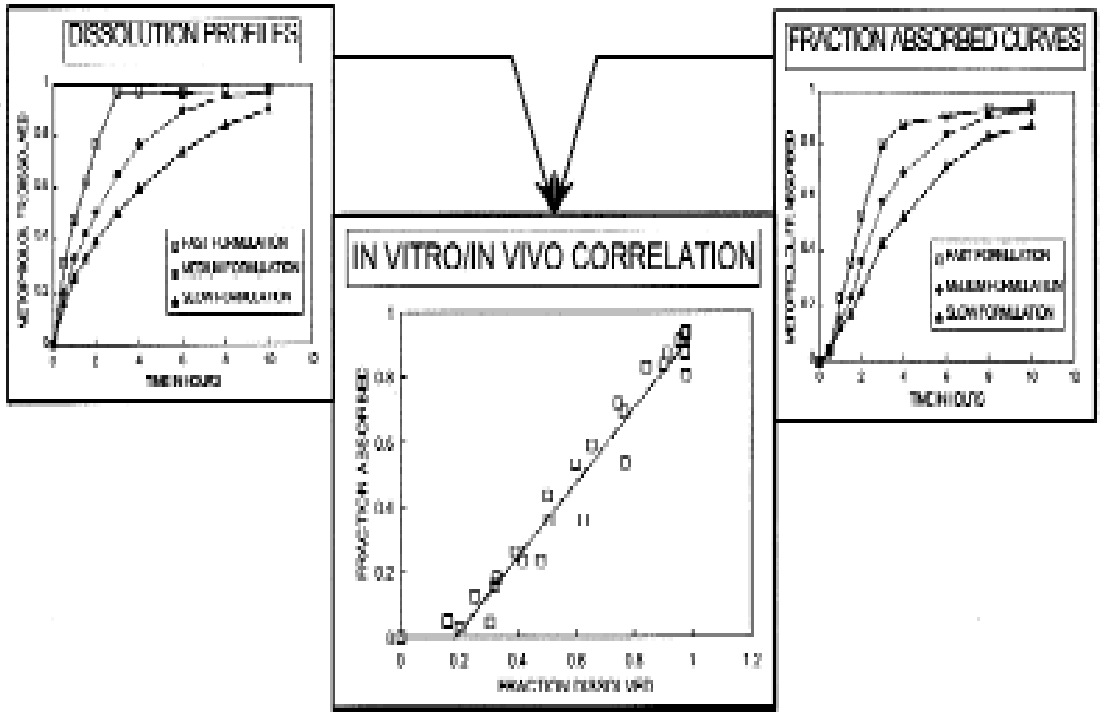


Fig. 2. Development of in vivo/in vitro correlation.

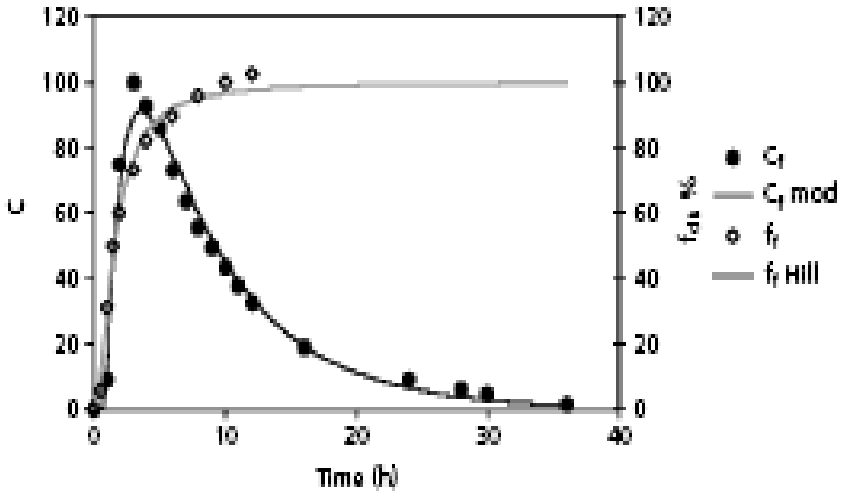
Journal of Controlled Release 72 (2001) 127–132
Regulatory perspectives on in vitro (dissolution) / in vivo (bioavailability) correlations
Venkata Ramana S. Uppoor

Convolution-based IVIVC methods

- Convolution-based IVIVC methods are one-stage modeling approaches, and they directly relate the time course of the in-vivo measured plasma concentration to the time profile of the in-vitro dissolution.
- integral or differential equations

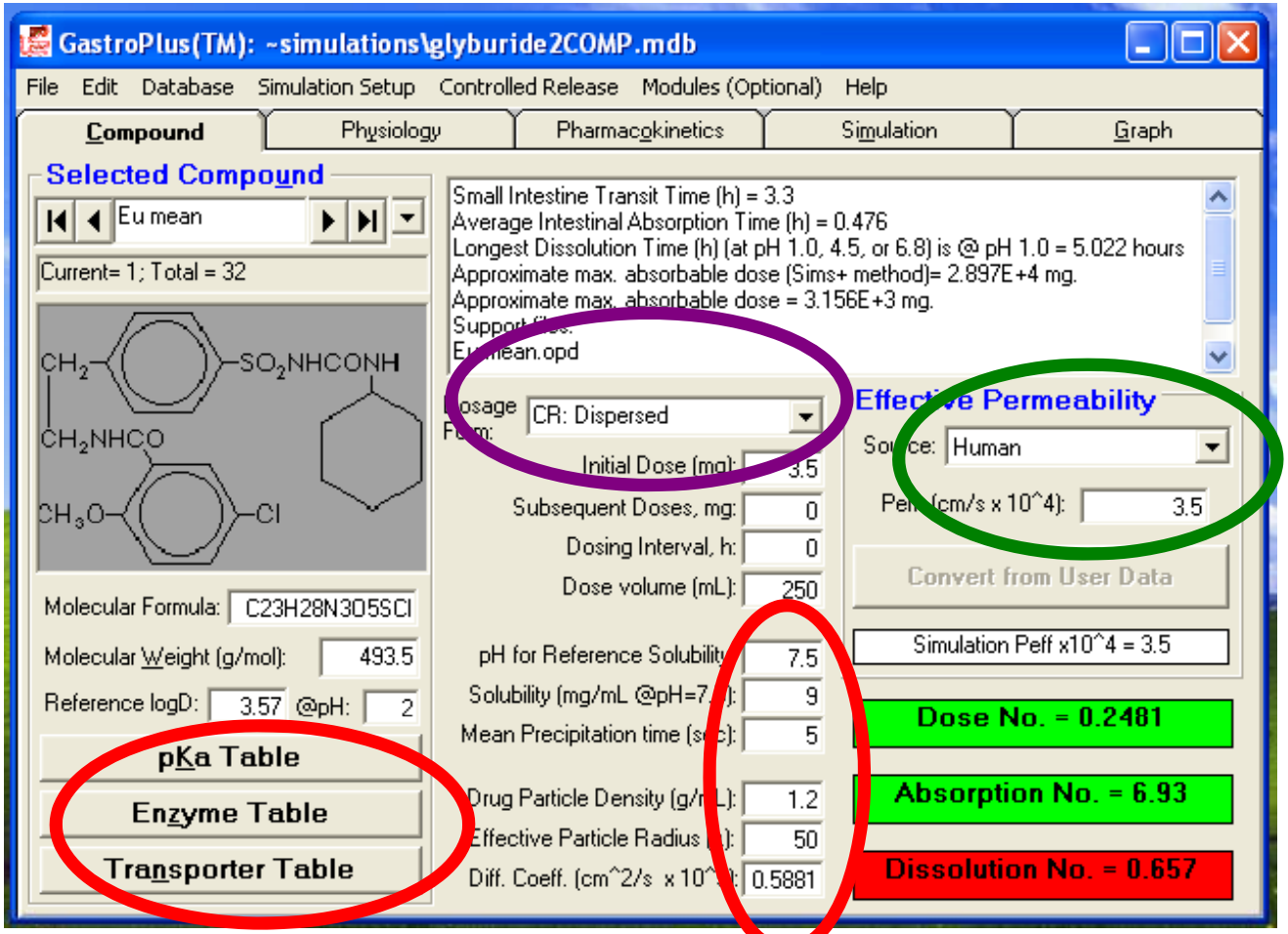
$$C(t) = r(t) * C_s(t) = \int_0^t C_s(t-\tau) r(\tau) d\tau$$

Gillespie 1997; Modi et al 2000; Veng-Pedersen et al 2000; Balan et al 2001; O'Hara et al 2001; Pitsiu et al 2001; Gomeni et al 2002



GastroPlus Software

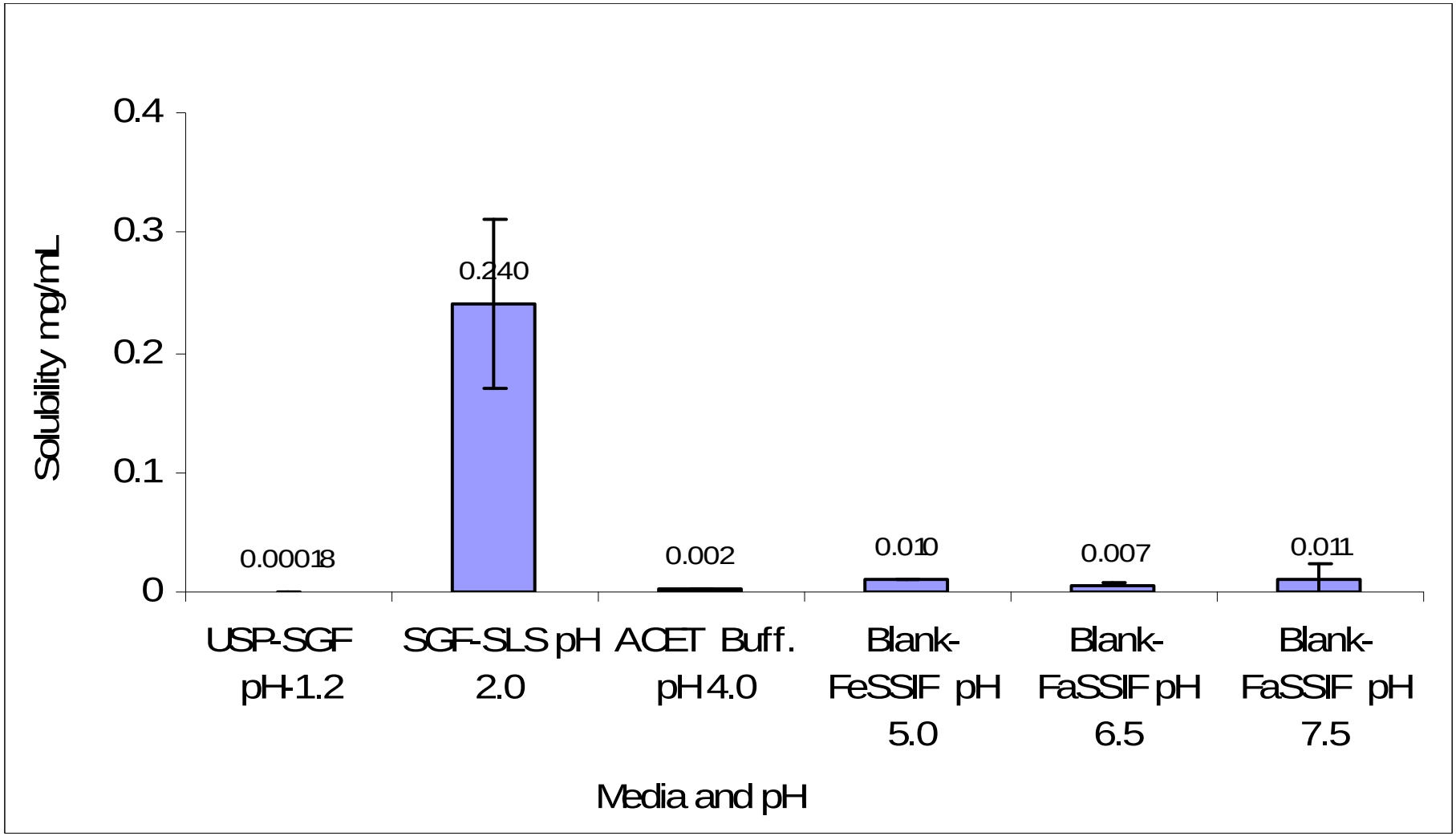
- Physicochemical Data as Input
- Dissolution Data as Input
- Permeability



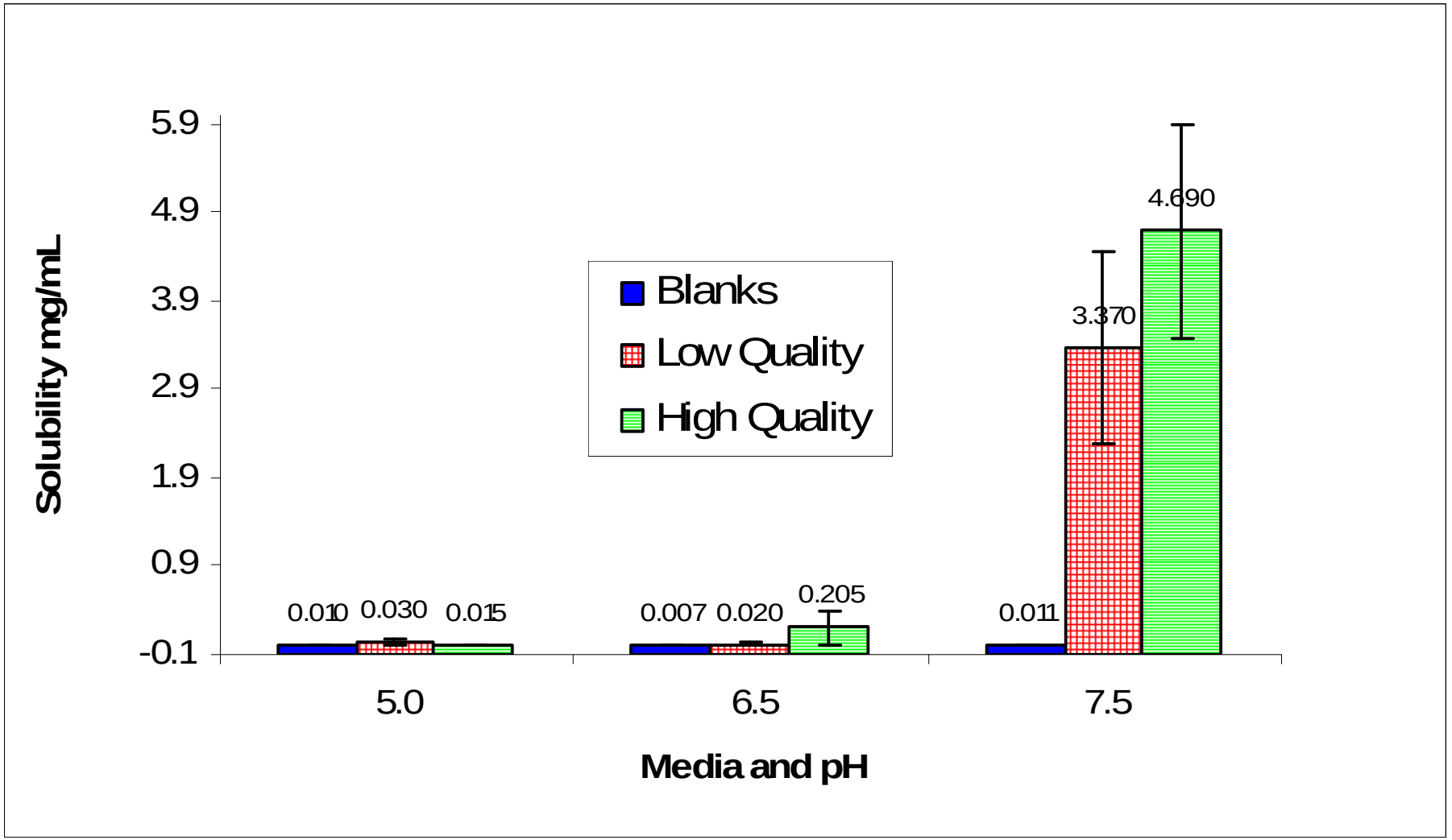
Dynamic Dissolution of a Lipophilic Drug

- pKa = 2.8 and 5.7 Basic and Acetic
- logP = 7.01, highly lipophilic
- >99% bound to plasma proteins
- Oral bioavailability variable 58-70%
  (Cheng, et al 1996)

Solubility in Blank Buffers



Solubility in Biorelevant media.

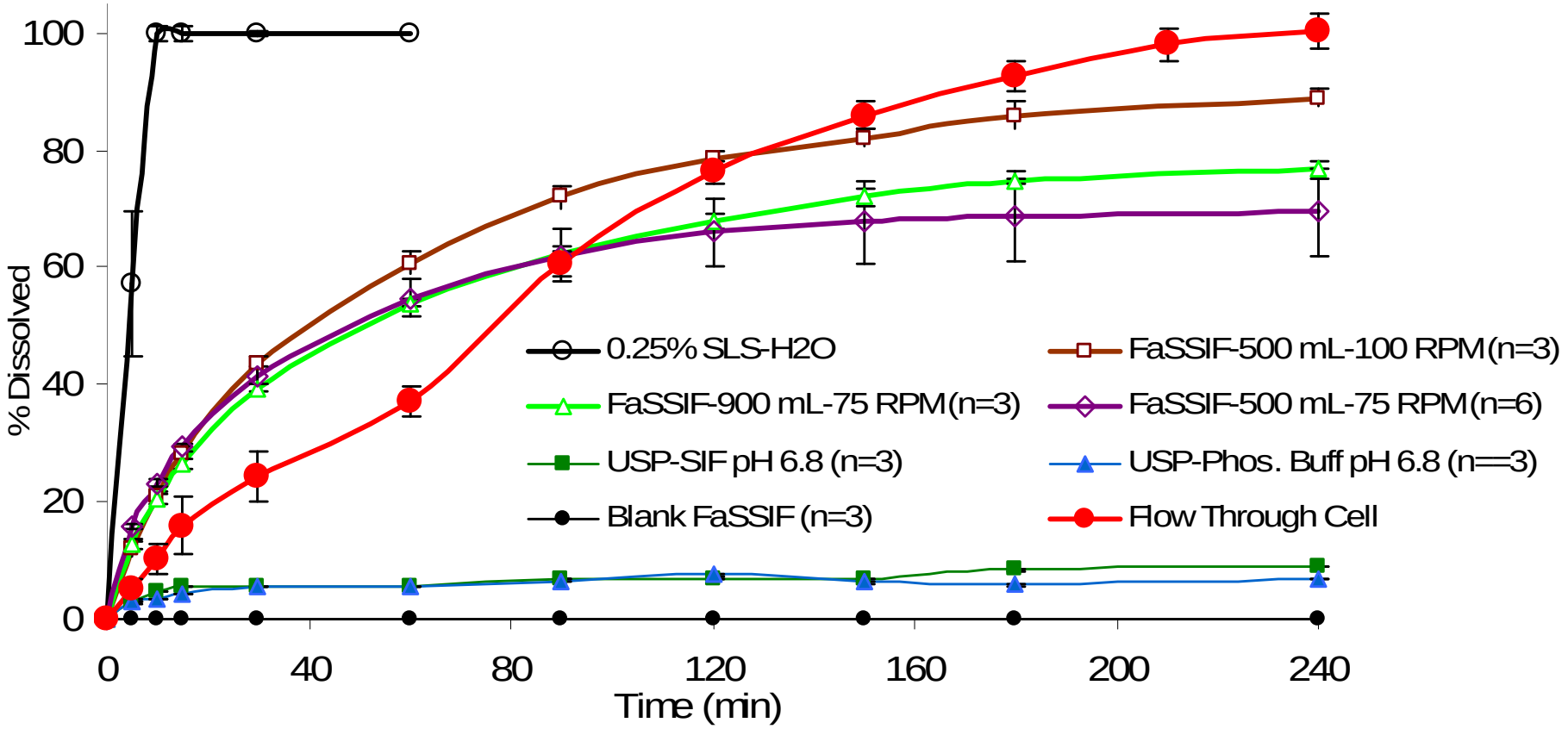


Dose/Solubility Ratio

			Dose (mg)	
			4	10
	pH	Solubility (mg/mL)	Dose/solubility ratio	
SGF (without enzymes)	1.2	0.00018	27777.8	55555.6
SGF-0.25% SLS	2.0	0.240	16.7	41.7
Acetate Buffer	4.1	0.002	2500.0	5000.0
LQ-FeSSIF	5.0	0.030	133.3	333.3
HQ-FeSSIF	5.0	0.015	266.7	666.7
LQ-FaSSIF	6.5	0.020	200.0	500.0
HQ-FaSSIF	6.5	0.205	19.5	48.8
LQ-FaSSIF	7.5	3.370	1.2	3.0
HQ-FaSSIF	7.5	4.690	0.9	2.1

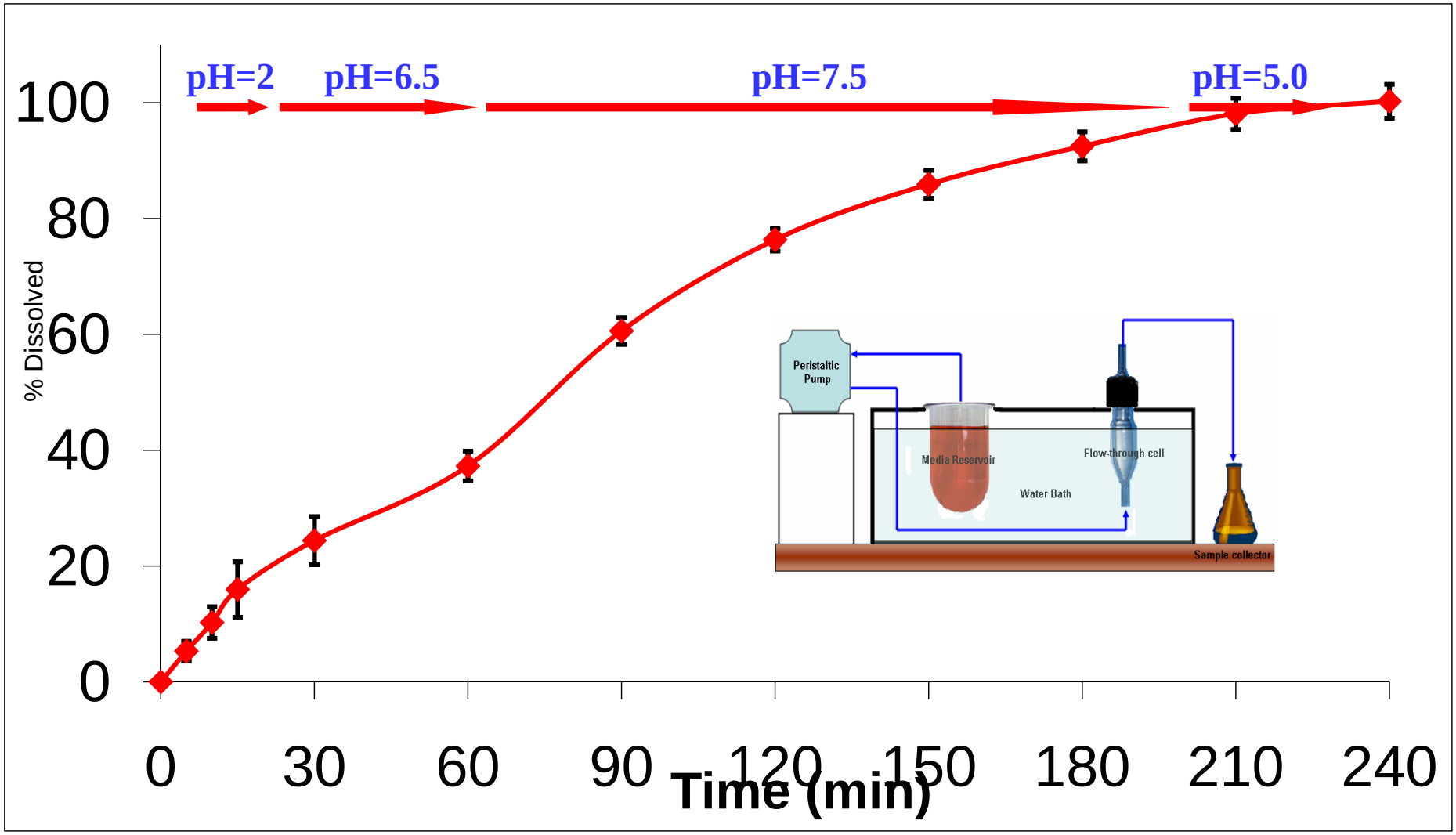
According to BCS, this drug is a poorly soluble drug

Dissolution Profiles



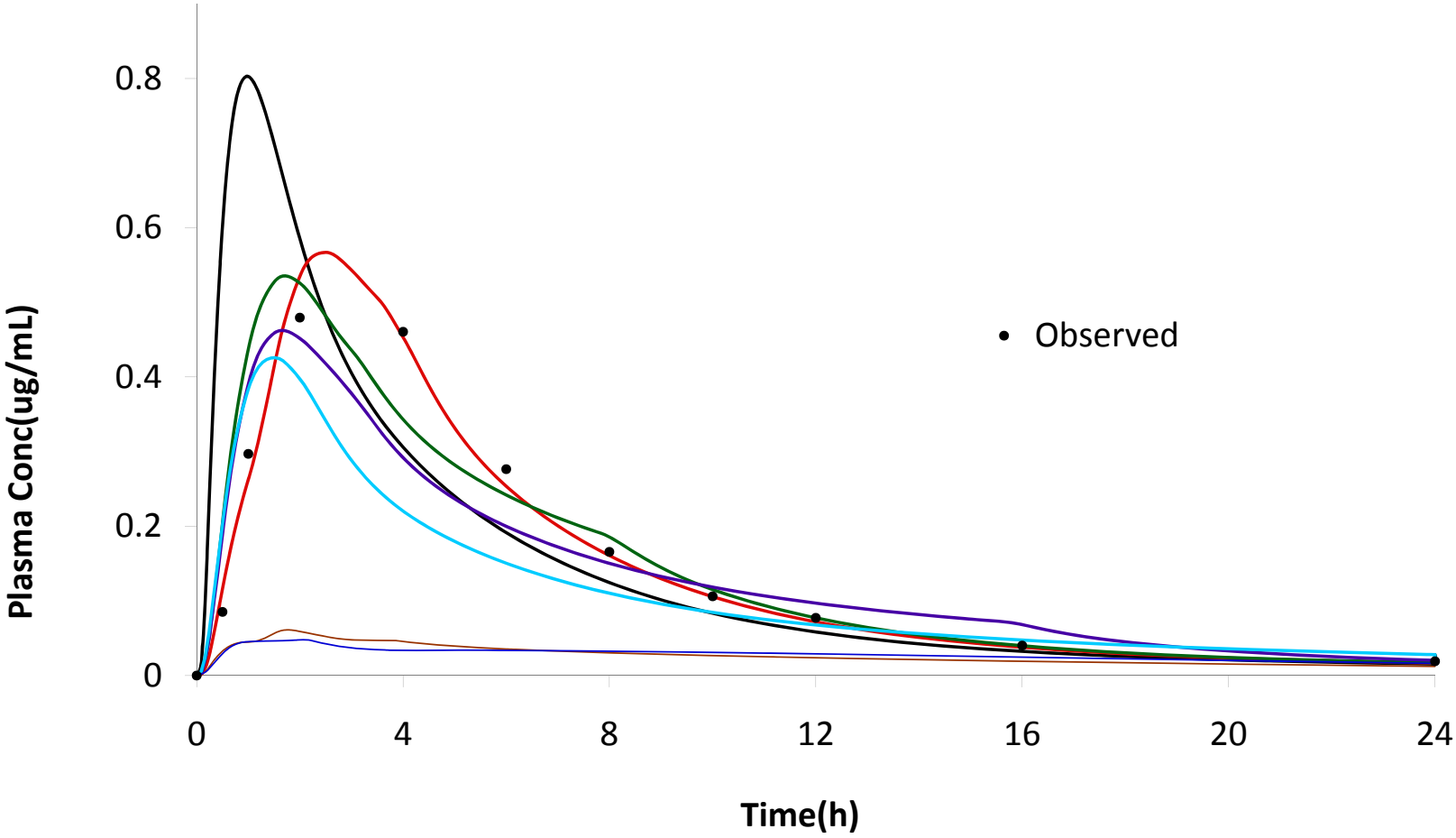
1. Fast and complete dissolution in 10 min H_2O-0.25% SLS.
2. Incomplete dissolution in biorelevant media (89, 77 and 69%) in FaSSIF 500-100 RPM, FaSSIF-900 & FaSSIF-500-75 RPM
3. SIF and Phosphate buffer <10%, and insignificant in blank FaSSIF
4. Insignificant difference between 500 and 900 mL at 75 RPM

Dynamic Dissolution



Dissolution rate relatively fast in SGF-SLS, **slows** down at **pH 6.5**, then increases when **pH** is Changed to **7.5**

Simulations Results



1. AUC from Flow through, FaSSIF-500 mL-100 RPM, FaSSIF-900 ml, 75 RPM and H2O-0.25% SLS are not significantly different from observed mean value ($p>0.05$)
2. Cmax from H2O-0.25% SLS is significantly different from observed mean value ($p<0.05$

Prediction error statistics

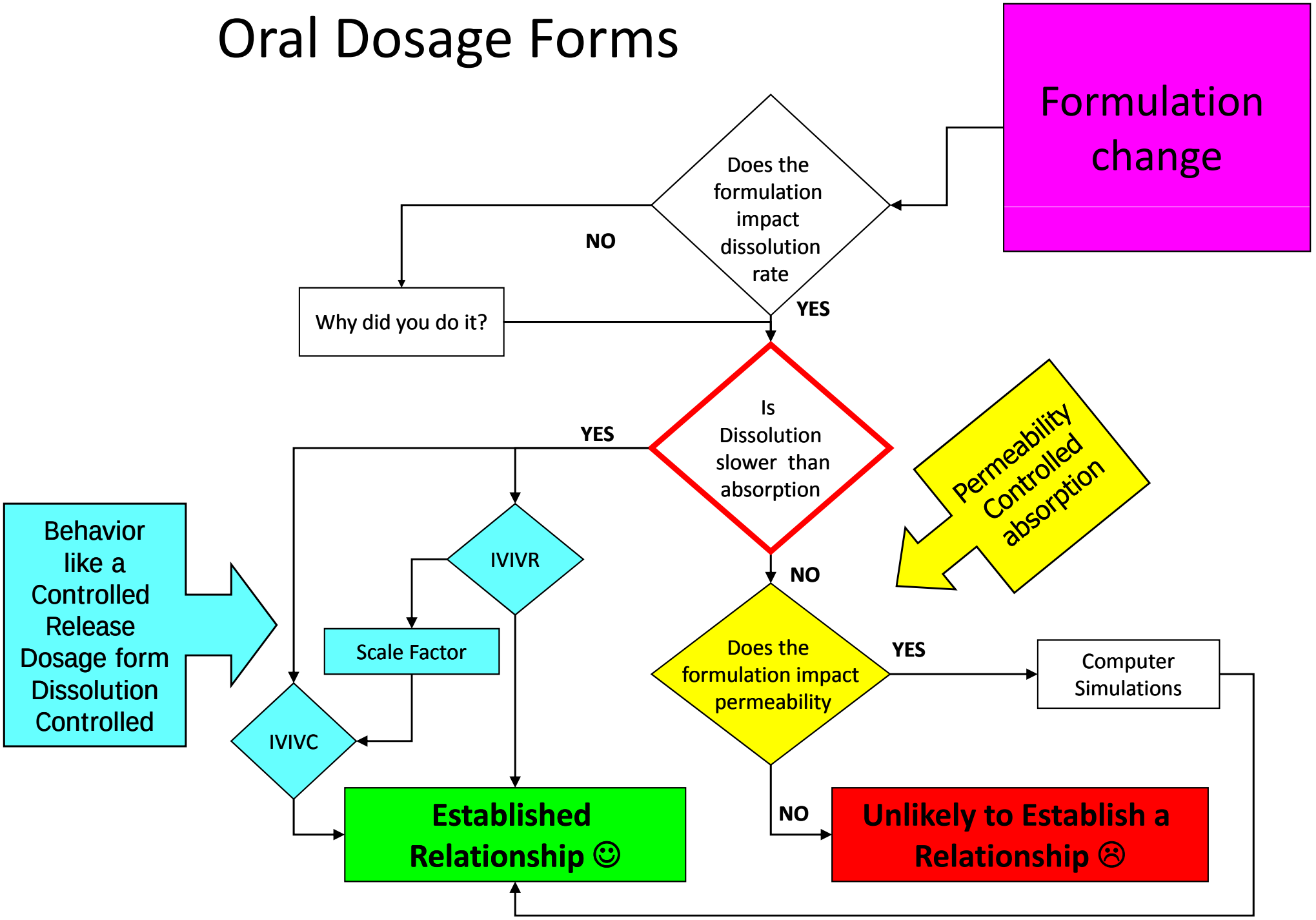
Observed values	*AUC=3.552 µg.h/mL*		*C_{max} =0.4796 µg/mL*	
	Predicted Values		AUC	C_{max}
Media	AUC (ug.h/mL)	C_{max} (ug/mL)	%PE	%PE
Flow through cells	3.52	0.567	1.0+	18.2*
FaSSIF-500 mL-100 RPM	3.49	0.535	1.7+	11.6*
FaSSIF-900 mL-75 RPM	3.31	0.462	6.9+	3.6+
FaSSIF-500 mL-75 RPM	2.68	0.426	24.5+	11.2+
USP-SIF	0.64	0.061	81.9+	87.3+
H2O-0.25% SLS	3.54	0.803	0.4*	67.4+
Flow thru-No FPE	5.67	0.913	59.6*	90.3*

***means %Higher**, and **+** means %**Lower** than mean **observed** value

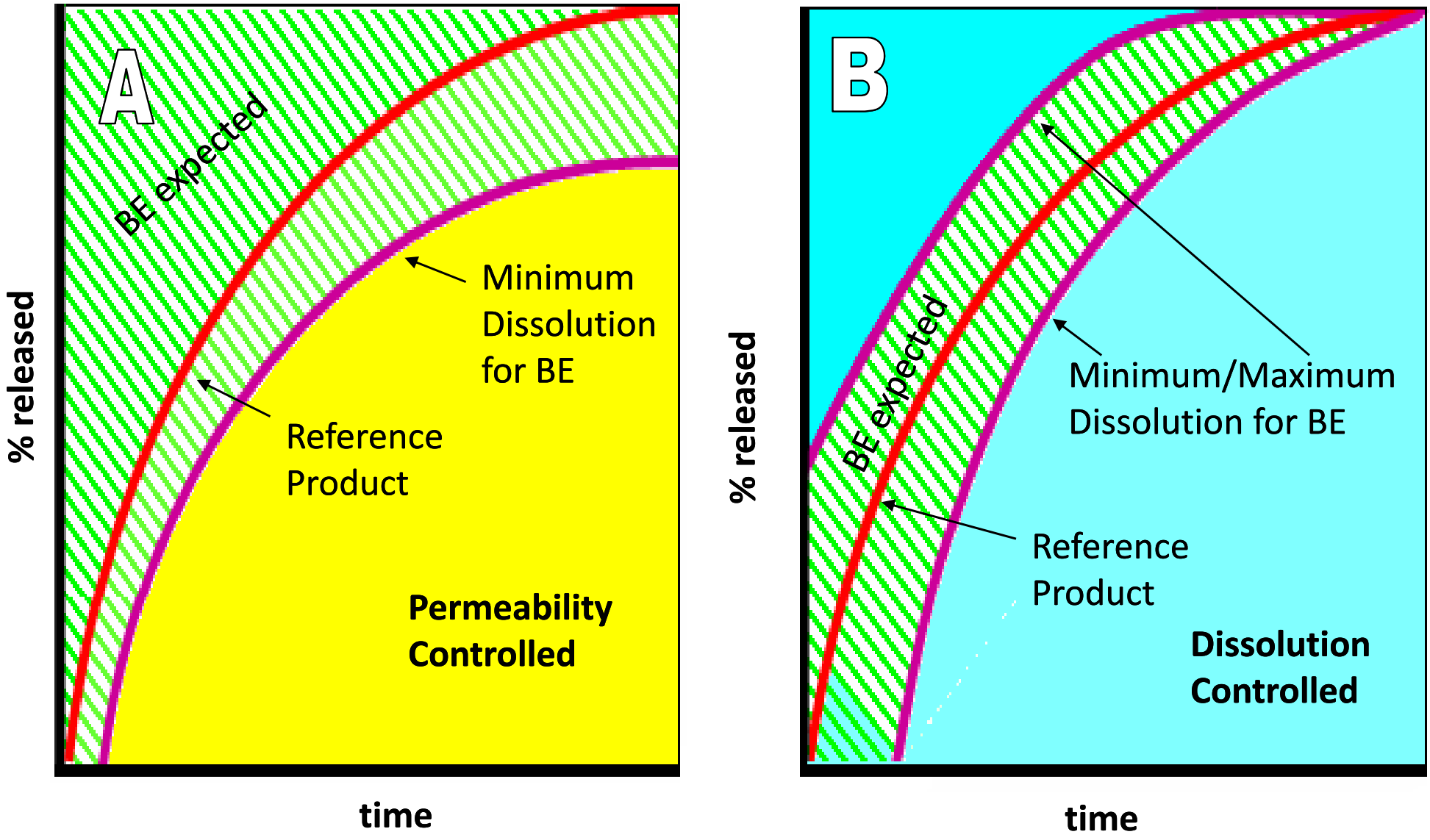
Example Conclusions

- Simulations showed that the drug is completely absorbed and throughout the GIT.
- Its bioavailability appears to be dissolution rate controlled.
- Level A IVIVC can best be established using the flow through cell dissolution
- The drug appears to be a BCS class 2 drug.

Oral Dosage Forms



Dissolution Requirements



Conclusions

- The BCS has changed the way we look at drugs and the drug development process
- The BCS is the mechanistic foundation for Biowaivers
- BCS is a risk management tool
- BCS allows us to ask the right questions to find the solutions in drug development
- Software can assist to estimate critical formulations variables
- Fewer in vivo studies
- QbD is a product specific extension of SUPAC
- Need to educate students in QbD

Acknowledgements

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- Dr. M. Di Maso
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