Graduate lecture at University of Maryland: on 17 August 2012
Update: 11 July 2013

BIOPHARMACEUTICS CLASSIFICATION SYSTEM: A BASIS FOR REGULATORY WAIVER OF IN VIVO BA/BE STUDIES

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Update

ViroPharma Suit Against FDA Over Generic Vancocin Tossed

[Bloomberg. By Andrew Zajac & Tom Schoenberg - Jan 9, 2013]

The company failed to produce new evidence following rejection in April of its request for a court order to block FDA approval of three generic versions of Vancocin

- *U.S. District Judge Ellen Segal Huvelle in Washington said today in her ruling.*
- The case is ViroPharma Inc. v. Hamburg, 12-cv-00584, U.S. District Court, District of Columbia(Washington)

Story of a Seminal Scientific Contribution & Its Regulatory Applications (1995-2000)

A theoretical basis for a biopharmaceutic drug classification: the correlation of in vitro drug product dissolution and in vivo bioavailability. Amidon GL, Lennernäs H, Shah VP, Crison JR. Pharm Res. 1995 Mar;12(3):413-20.

- Regulatory applications
  - *1995: SUPAC IR*
  - *2000: "Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System" (August 2000)*
  - *Future applications?*

What is BCS?

A paradigm shift

http://www.fda.gov/ohrms/dockets/ac/04/slides/2004-4078S2_10_Amidon_files/frame.htm

- $M(t) = \iiint_0^t PC(\frac{dA}{dt})$
- $K_a = (\frac{S}{V})P_{eff}$
- $Absorption\ number\ A_n = \frac{Peff}{R}.< T_{si} >$
- $Dissolution\ number D_n = \left(\frac{3D}{r^2}\right)\left(\frac{C_s}{\rho}\right).< T_{si}>$
- If the Peff of a drug is less than2•10–4 cm/s, then drug absorption will be incomplete
- Class I—high solubility, high permeability: generally very well-absorbed compounds
- Class II—low solubility, high permeability: exhibit dissolution rate-limited absorption
- Class III—high solubility, low permeability: exhibit permeability rate-limited absorption
- Class IV—low solubility, low permeability: very poor oral bioavailability

Journal of Clinical Pharmacology, 2002;42:620-643

Regulatory Applications?

Initial application in SUPAC-IR (1995)	• Types of dissolution test comparisons for manufacturing and formulation changes
Waiver of In vivo BA/BE …BCS Guidance (2000)	• Methods to classify per BCS and criteria for biowaiver
Efforts to extend biowaivers (beyond 2000)	• Several workshops and reports
A relatively recent application to a 'locally acting' drug	• Debate and court case
Opportunities for Quality by Design	• BCS a foundational element of QbD

Learning objectives

Broadly, gain an understanding of considerations for translating scientific knowledge into regulatory policy

(1). Considerations for developing the FDA guidance
"Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System" (August 2000)

Develop a basis to critically evaluate considerations utilized for development of the FDA guidance document

(2) What questions should you ask?

(3) What assumptions should you accept?

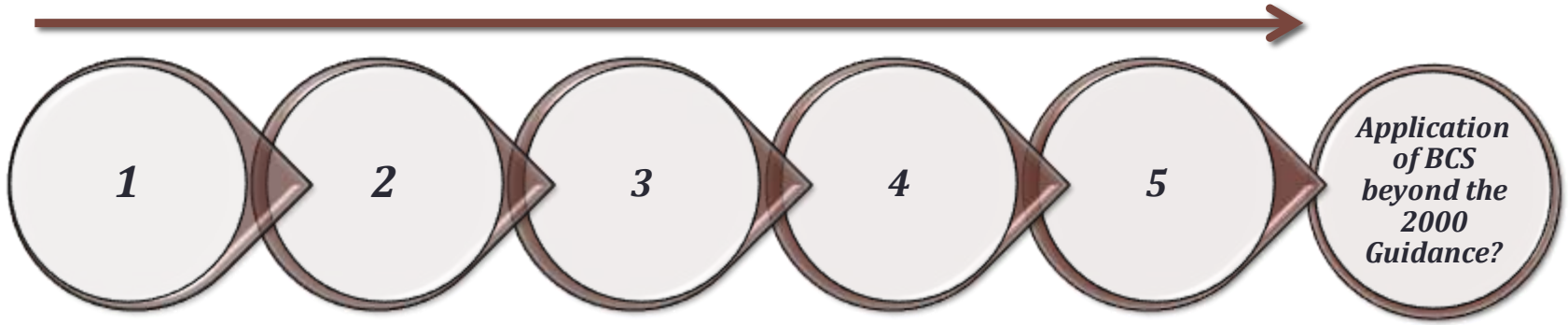
(4) How precise should your answers be?

Identify and explain how future regulatory applications of BCS may be realized in the context of 'Quality by Design'

(5) How should you 'connect the dots': CMC – BA/BE?

Can you justify new applications of BCS (i.e., beyond the 2000 guidance)?

Presentation outline



VIROPHARMA INCORPORATED, Plaintiff,
Vs.
MARGARET A. HAMBURG, M.D., et al., Defendants.

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA
Civil Action No. 12-cv-00584-ESH
Filed 04/17/12

VIROPHARMA INC., PLAINTIFF, VS. (FDA) MARGARET A. HAMBURG, M.D., ET AL., DEFENDANTS.

IN THE UNITED STATES DISTRICT COURT FOR THE DISTRICT OF COLUMBIA

Civil Action No. 12-cv-00584-ESH

Filed 04/17/12

13 April 2012 Plaintiffs sued FDA

Issue

- Agency's 9 April 9 2012 approval of three ANDAs of the company's Vancocin® (vancomycin hydrochloride).

They alleged that:

- FDA impermissibly interpreted the Food, Drug, and Cosmetic Act when it denied the company three-year exclusivity for its NDA supplement ("sNDA") ("exclusivity claim"); and
- FDA violated its own regulations—and changed established policy without the procedure required by law—when it chose to accept in vitro bioequivalence data for oral vancomycin ("bioequivalence claim").

http://www.fdalawblog.net/fda_law_blog_hyman_phelps/2012/04/court-denies-viropharmas-motion-for-tropi-in-vancomycin-caseleaves-generics-on-the-market.html

23 April 2012 Memorandum of Opinion

The Judge

http://en.wikipedia.org/wiki/Ellen_Segal_Huvelle#Early_life_and_career

and citation omitted). Especially given the scientific expertise driving the FDA's well-reasoned decision in this matter, *see Serono Labs.*, 158 F.3d at 1320, the Court concludes that ViroPharma is unlikely to prevail on the merits of its bioequivalence claim. The FFDCA and a number of the FDA's own regulations grant the agency wide discretion in "determin[ing] whether bioequivalence has been established." *Bristol-Myers Squibb Co. v. Shalala*, 923 F. Supp. 212, 217 (D.D.C. 1996).[27] Furthermore, in addition to the provision on which the agency specifically relied, 21 C.F.R. § 320.22(e), "waivers" of any *in vivo* bioequivalence requirement for ANDAs may be permitted pursuant to, *inter alia*, §§ 320.21(b)(2), 320.21(f), 320.22, and 320.24(b)(6). Where the regulations allow so many "waivers," the "default" position that ViroPharma argues is difficult to discern.[28] In light of the deference owed, the Court has no basis for overruling the

Memorandum Opinion issued on April 23, 2012

TITLE 21--FOOD AND DRUGS
CHAPTER I--FOOD AND DRUG ADMINISTRATION
SUBCHAPTER D--DRUGS FOR HUMAN USE

- PART 320 BIOAVAILABILITY AND BIOEQUIVALENCE REQUIREMENTS
- **Subpart A--General Provisions**
  § 320.1 - Definitions.
- **Subpart B--Procedures for Determining the Bioavailability or Bioequivalence of Drug Products**
  § 320.21 - **Requirements for submission of bioavailability and bioequivalence data**.
  § 320.22 - **Criteria for waiver of evidence of in vivo bioavailability or bioequivalence**.
  § 320.23 - Basis for measuring in vivo bioavailability or demonstrating bioequivalence.
  § 320.24 - **Types of evidence to measure bioavailability or establish bioequivalence.**
  § 320.25 - Guidelines for the conduct of an in vivo bioavailability study.
  § 320.26 - Guidelines on the design of a single-dose in vivo bioavailability or bioequivalence study.
  § 320.27 - Guidelines on the design of a multiple-dose in vivo bioavailability study.
  § 320.28 - Correlation of bioavailability with an acute pharmacological effect or clinical evidence.
  § 320.29 - Analytical methods for an in vivo bioavailability or bioequivalence study.
  § 320.30 - Inquiries regarding bioavailability and bioequivalence requirements and review of protocols by the Food and Drug Administration.
  § 320.31 - Applicability of requirements regarding an "Investigational New Drug Application."
  § 320.32 - Procedures for establishing or amending a bioequivalence requirement.
  § 320.33 - Criteria and evidence to assess actual or potential bioequivalence problems.
  § 320.34 - Requirements for batch testing and certification by the Food and Drug Administration.
  § 320.35 - Requirements for in vitro testing of each batch.
  § 320.36 - Requirements for maintenance of records of bioequivalence testing.
  § 320.38 - Retention of bioavailability samples.
  § 320.63 - Retention of bioequivalence samples

http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=320.22

Draft Guidance on Vancomycin Hydrochloride (2008)

Vancomycin HCl Capsules are administered orally for treatment of enterocolitis	• Vancomycin acts locally in the lower GI tract • The dosage form is expected to be in contact with a relatively large fluid volume, vancomycin is expected to be in solution long (e.g., hours) before it reaches the site of action in the lower GI tract.
The BE of two capsule formulations of oral vancomycin HCl is determined by?	• Equivalent release of vancomycin, • The high solubility of vancomycin drug substance, • The effect of inactive ingredients on the transport of vancomycin drug through the GI tract and/or the effectiveness of drug at the site of action
In Vitro BE	• Formulations are Q1 and Q2 the same as the RLD • Dissolution: Basket, 100 rpm, 0.1N HCl (or 0.1N HCl with NaCl at pH 1.2), pH 4.5 Acetate buffer, and pH 6.8 Phosphate buffer; 900 mL; 37ºC • An f2 test of similarity

http://www.fda.gov/OHRMS/DOCKETS/98fr/FDA-2008-D-0626-gdl.pdf

Plaintiffs' Argument Prior to the Court Case

30 June 2009, Plaintiffs' briefing document FDA Advisory Committee for Pharmaceutical Science and Clinical Pharmacology

"Is essentially the Biopharmaceutics Classification System (BCS)-based biowaiver, which was developed using healthy GI parameters to predict the absorption of systemically acting drugs from the healthy gut and was not intended for use in predicting the in vivo performance of locally acting GI drugs"

Healthy GI physiological parameters may not be an appropriate in vitro model for assessing BE with locally acting GI drugs used to treat serious GI disease

Oral Vancomycin is Systemically Absorbed in Some Patients and has Been Linked with Systemic Toxicity. Does a Biowaiver Ensure Safety or Should In Vivo Testing be Considered for this Drug?

Extension of a Biowaiver to a New Class of Drug Should be Evidence-Based and Data-Driven.

Evaluation of Inactive Ingredients

http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AdvisoryCommitteeforPharmaceuticalScienceandClinicalPharmacology/UCM173159.pdf

www.fda.gov/downloads/AdvisoryCommittees/.../UCM179424.pdf (FDA ACPS Transcripts)

Plaintiffs , In-Part, Based their Arguments on a Previous ACPS Discussion (October 20, 2004)

Bioequivalence Testing for Locally Acting Gastrointestinal

ACPS presentations: Prof. Amidon
http://www.fda.gov/ohrms/dockets/ac/04/slides/2004-4078S2_10_Amidon_files/frame.htm

and OGD (Lionberger)
http://www.fda.gov/ohrms/dockets/ac/04/slides/2004-4078S2_11_Lionberger_files/frame.htm

As the Deputy Director of FDA's Office of Pharmaceutical Science Dr. Ajaz Hussain summarized in his concluding remarks, "I don't want to sort of jump in and say all right" and simply apply the BCS approach to locally acting GI drugs, in part because issues relating to "volume" and "hydrodynamics" merited close attention. Consequently, he said, "we have to give some thought to how we would approach that, so it is not a trivial matter."
(http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AdvisoryCommitteeforPharmaceuticalScienceandClinicalPharmacology/UCM173159.pdf)

My comments (cited) related to broad policy decision; not relevant to specific case example as in this case.

FDA 'point-to-point' response to the Citizen Petition addressed the questions posed

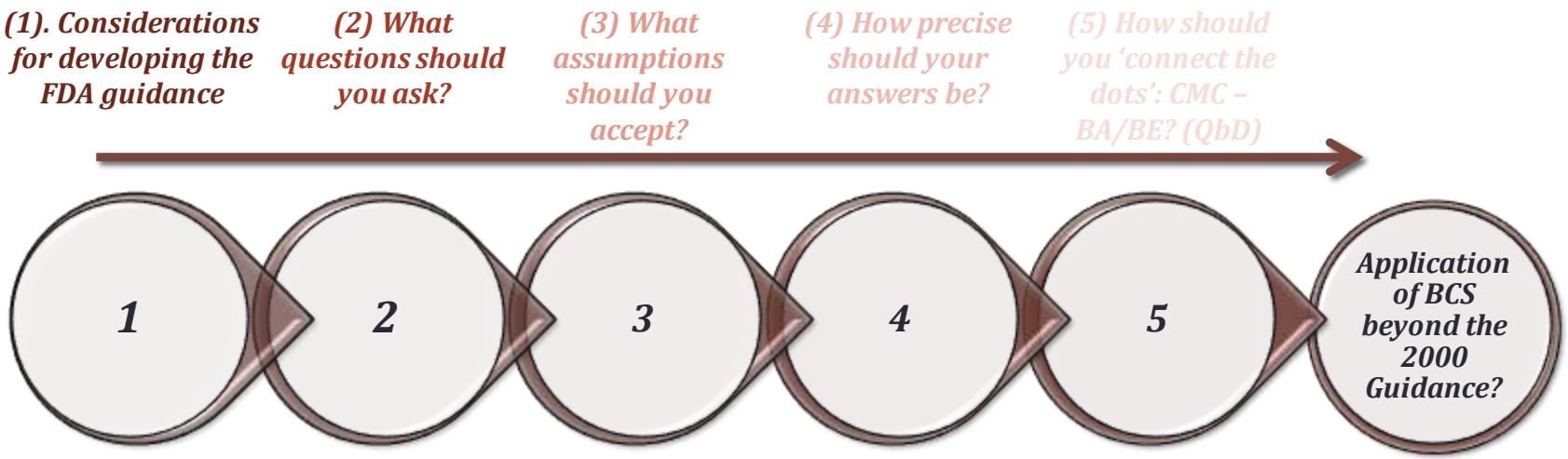
http://www.regulations.gov/#!documentDetail;D=FDA-2006-P-0007-0051

Congressional Record - Senate (S5649-5650), May 7, 2007 - [D. Robertson - Comment]

http://www.regulations.gov/#!documentDetail;D=FDA-2006-P-0007-0014

http://www.fda.gov/ohrms/dockets/ac/04/transcripts/2004-4078T2.pdf (ACPS 2004 transcripts)
http://www.regulations.gov/#!documentDetail;D=FDA-2006-P-0007-0051 (FDA CP response)

Re-cap and Next Steps



A successful application of BCS principles to a particular "locally acting" drugs (low to no permeability). FDA willing to make 'case-by-case' decision. Broad policy recommendation yet to be formulated.

CONSIDERATIONS FOR DEVELOPING THE FDA GUIDANCE: QUESTIONS, ASSUMPTIONS, AND NEEDED PRECISION

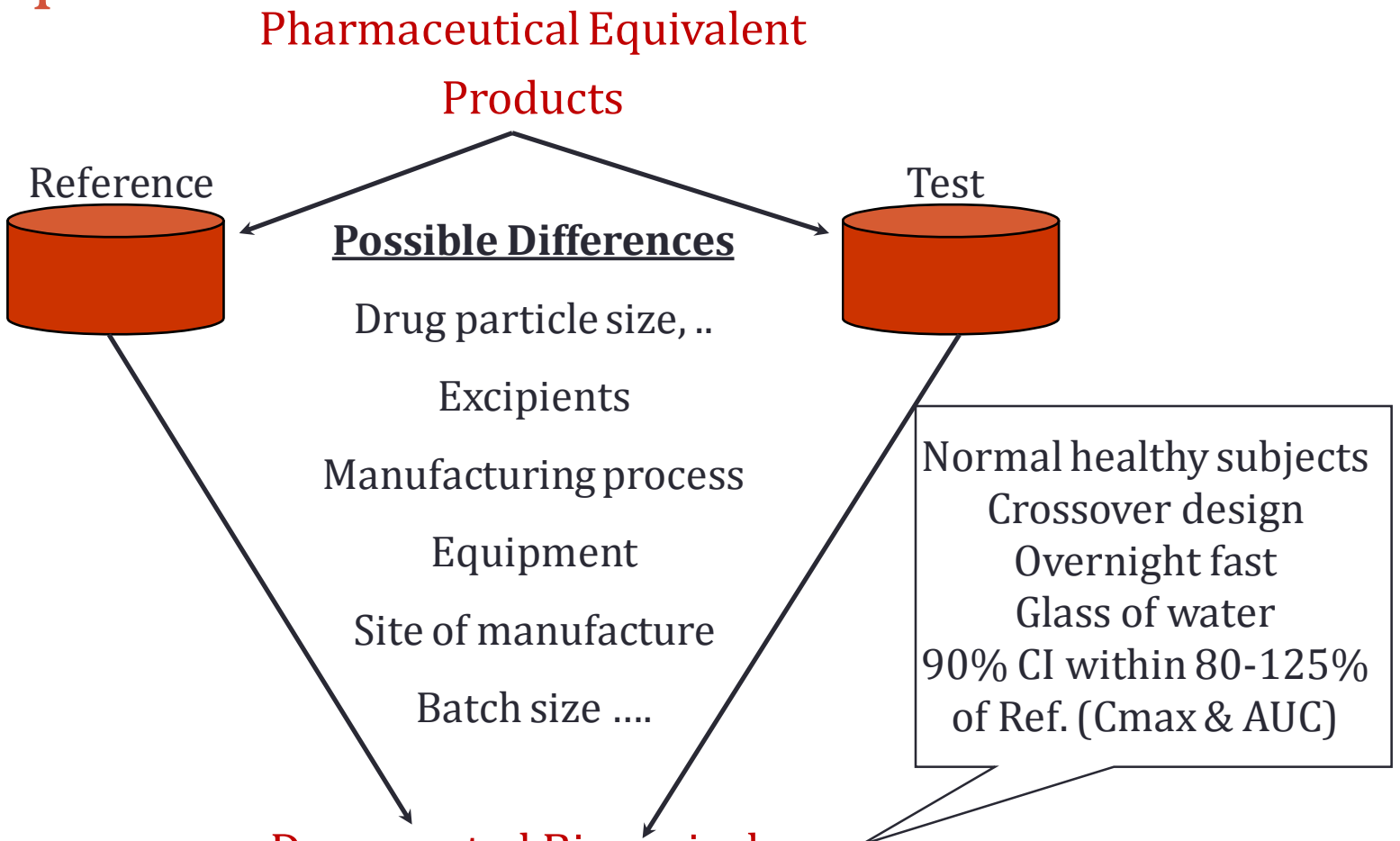
Reflecting back to 1995-2000

Note: A number of data slides to follow have been taken from a previous presentation available at:
*www.**fda**.gov/ohrms/dockets/ac/05/.../2005-4137S2_02_**Hussain**.ppt*

Need to Reduce Our Reliance on *In Vivo* BE Studies: Why?

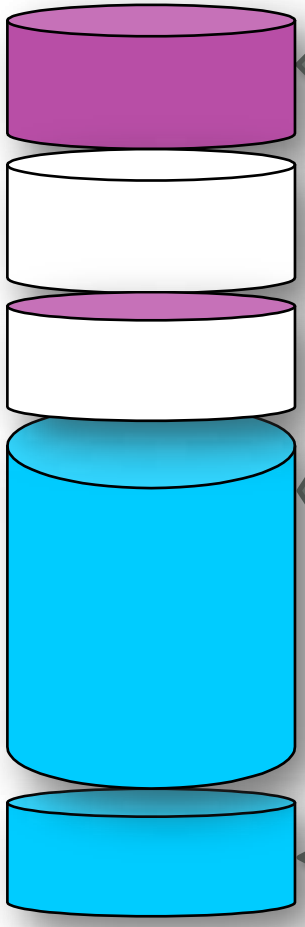
Ethical reasons	• 21 CFR 320.25(a) "… no unnecessary human research should be done."
Focus on prevention	• "building quality into products" • "right first time"
Efficiency	• Science continues to provide new methods to identify and eliminate unnecessary *in vivo* BE studies; reduce time and cost of drug development and review

Therapeutic Equivalence



(Note: Generally, same dissolution spec.)

Regulatory Bioequivalence: A Summary



Solutions

Suspensions

Chewable, etc.

Conventional Tablets Capsules

MR Products

"Self-evident" - Biowaivers granted
Condition- excipients do not alter absorption (historical data)

Pre-1962 DESI Drugs: In Vivo evaluation for "bio-problem" drugs (TI, PK, P-Chem)
Post-1962 Drugs: Generally In Vivo - some exceptions (IVIVC..)

SUPAC-IR (1995)
Dissolution-IR
BCS
(pre-/post approval

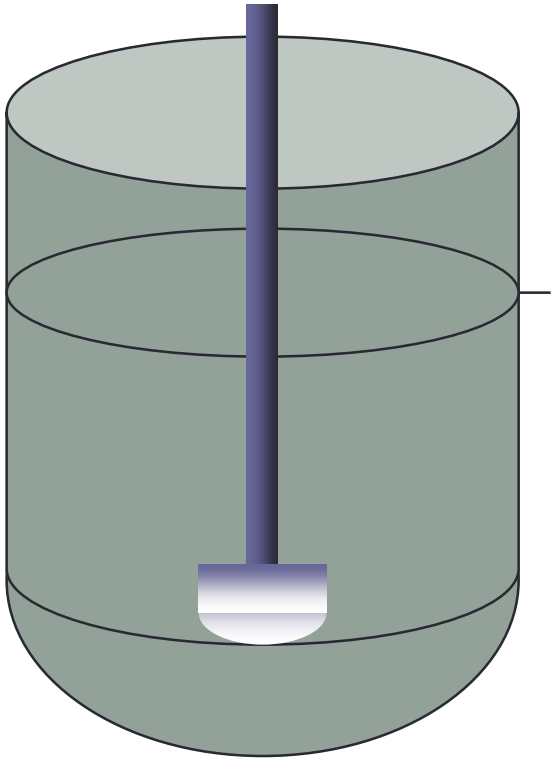
In Vivo BE

SUPAC – MR; IVIVC

IVIVC = In vitro to in vivo correlation

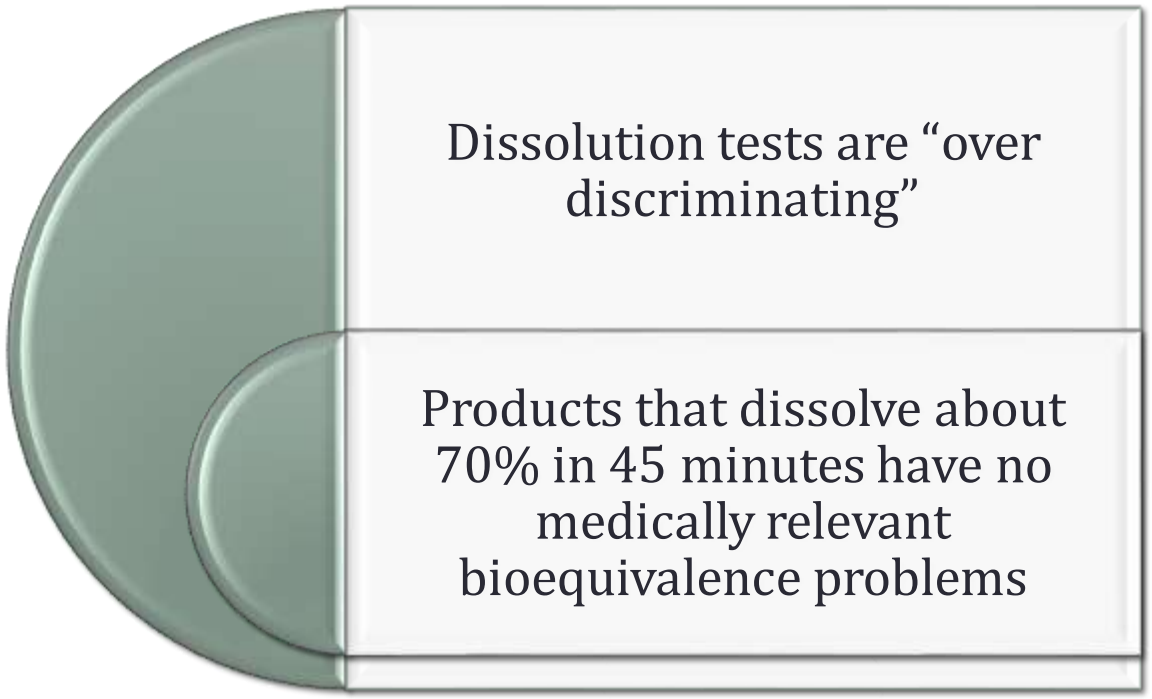
Quality by Design & Design Space

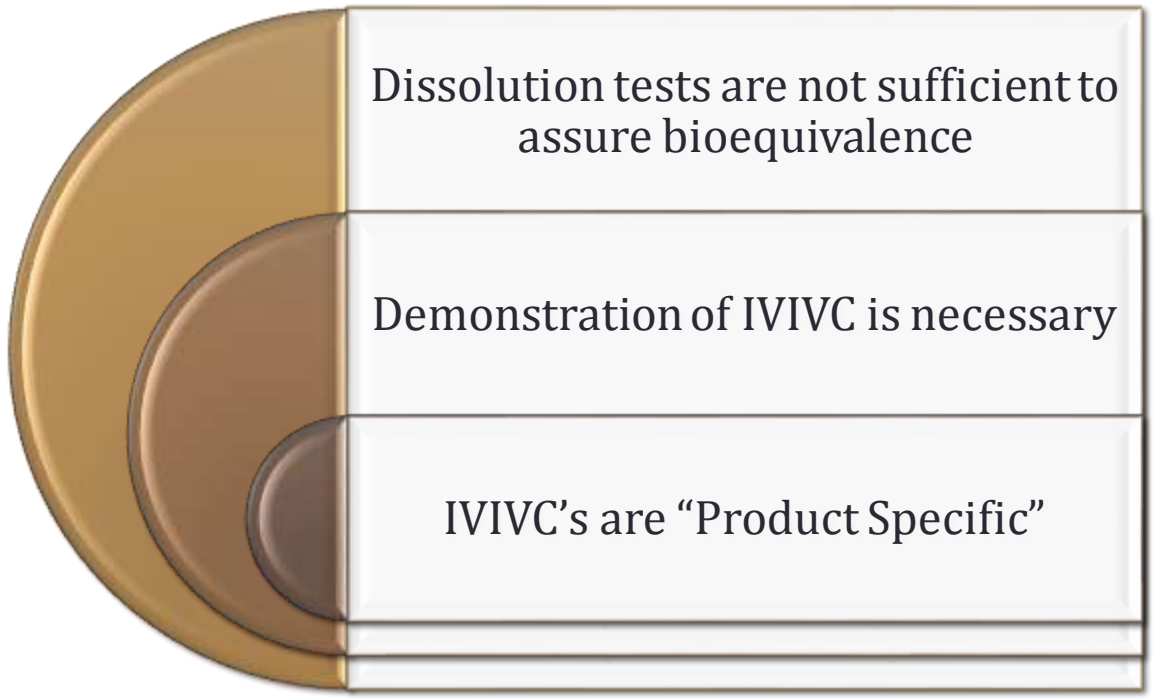
Dissolution Test Methods



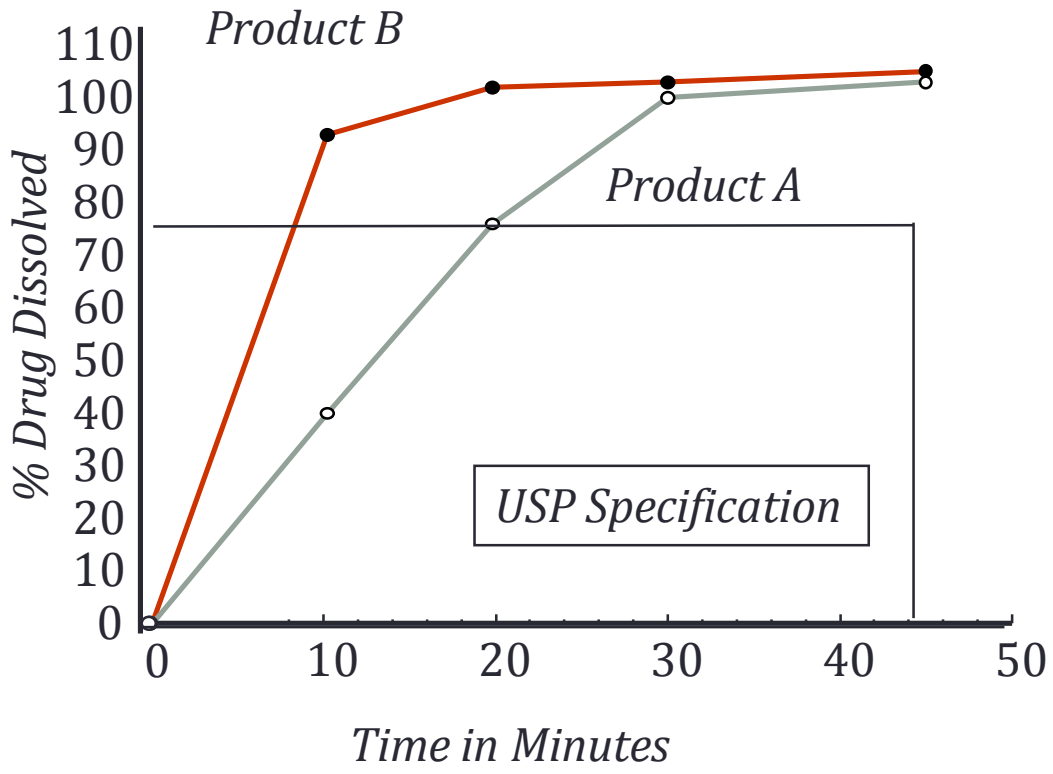
> 900 ml, 37°C
> Water, 0.1 N HCl, pH 6.8 buffer, or…
> 50 rpm (paddle), 100 rpm (basket),…
> Vessel geometry
> Location of dosage unit

Dissolution tests: Debates





Failure to Discriminate Between Bio-in-equivalent Products: Inappropriate Acceptance Criteria



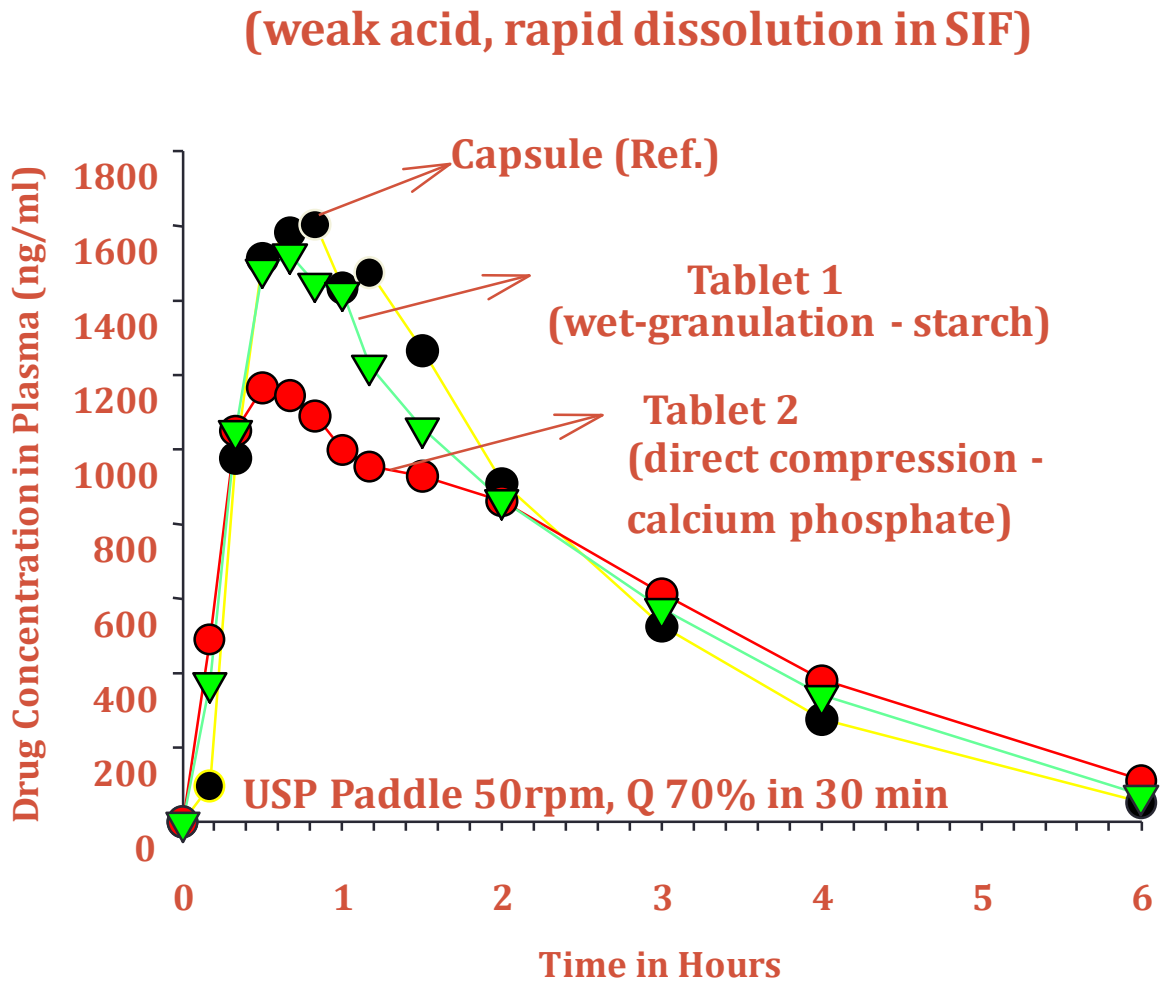
Product B was not bioequivalent to Product A

Log(AUCinf): CI 94.6 - 123.6

Log(AUC): CI 89.1 - 130.0

Cmax: CI 105.3 - 164.2

Failure to Discriminate Between Bio-in-equivalent Products: Inappropriate Test Method?



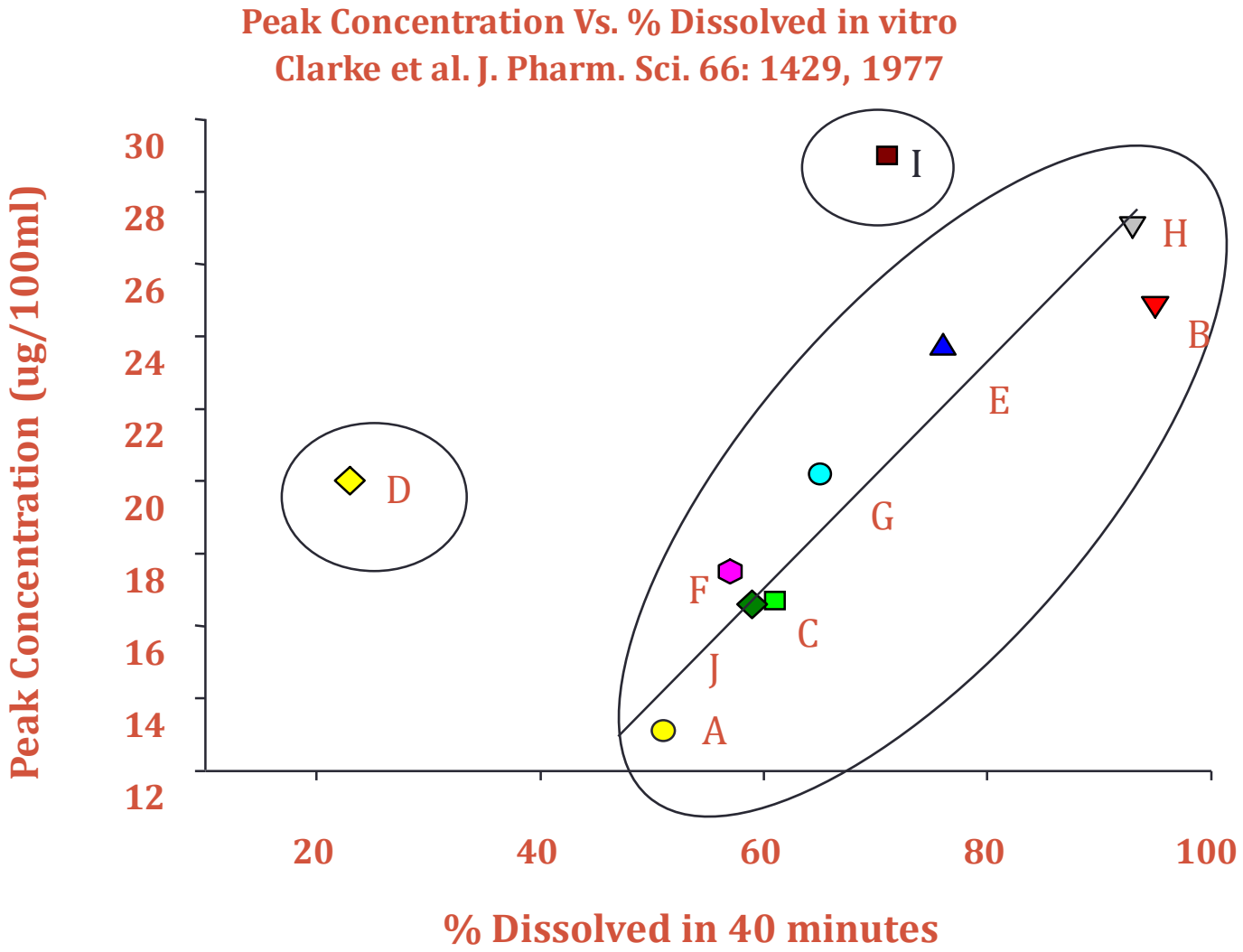
Dissolution Test Problems: False +ives and -ives

Test/Ref. Mean

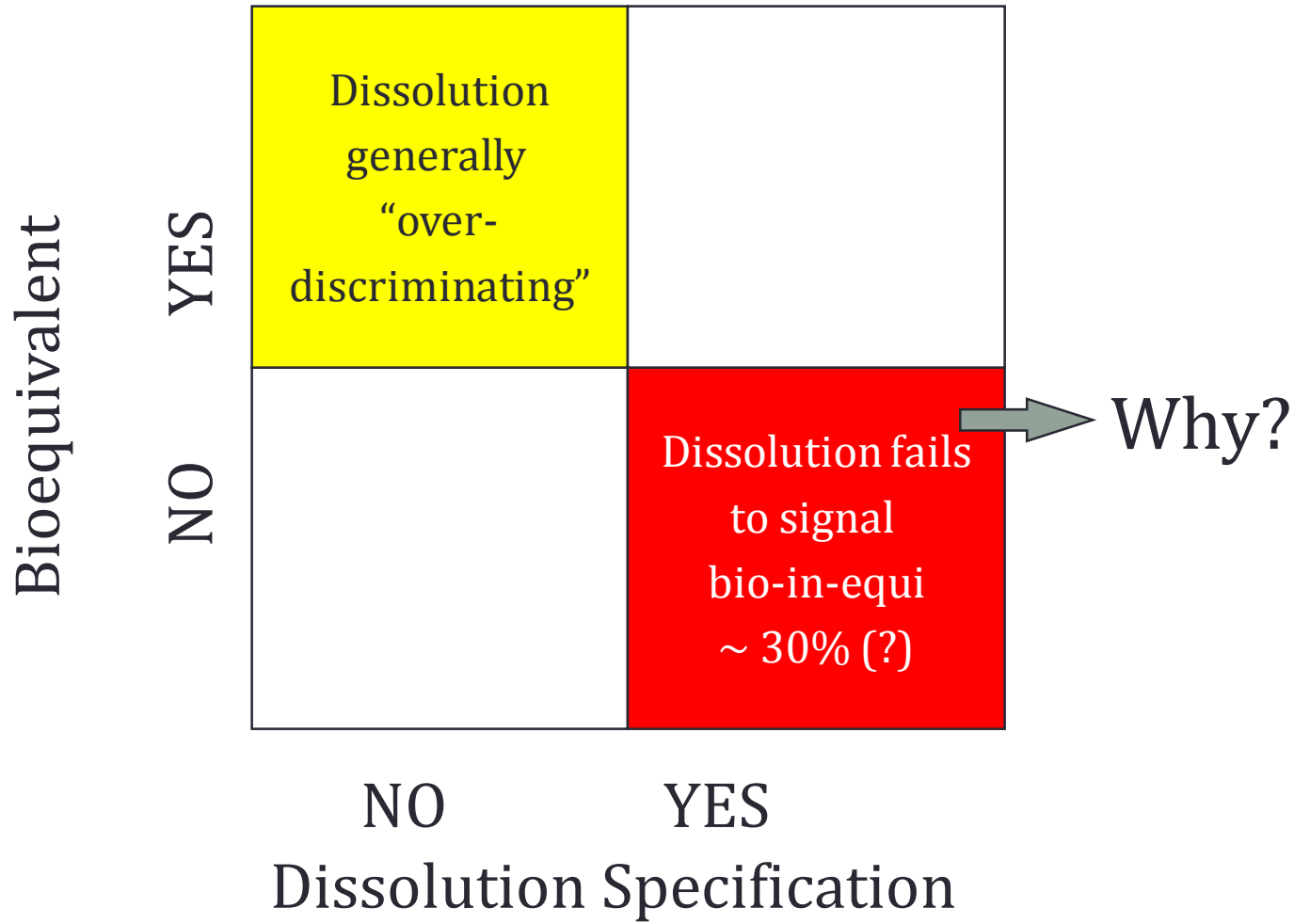
	15 min	*30 min*	*45 min*	*AUC*	*Cmax*
Ref	95	96	98	100	100
B	96	97	97	104	95
C	62	84	92	84	55
D	82	94	95	88	87
E	103	103	103	112	120
F	13	35	53	100	102

I. J. MacGilvery. Bioequivalence: A Canadian Regulatory Perspective. In, Pharmaceutical Bioequivalence . Eds. Welling, Tse, and Dighe. Marcel Dekker, Inc., New York, (1992).

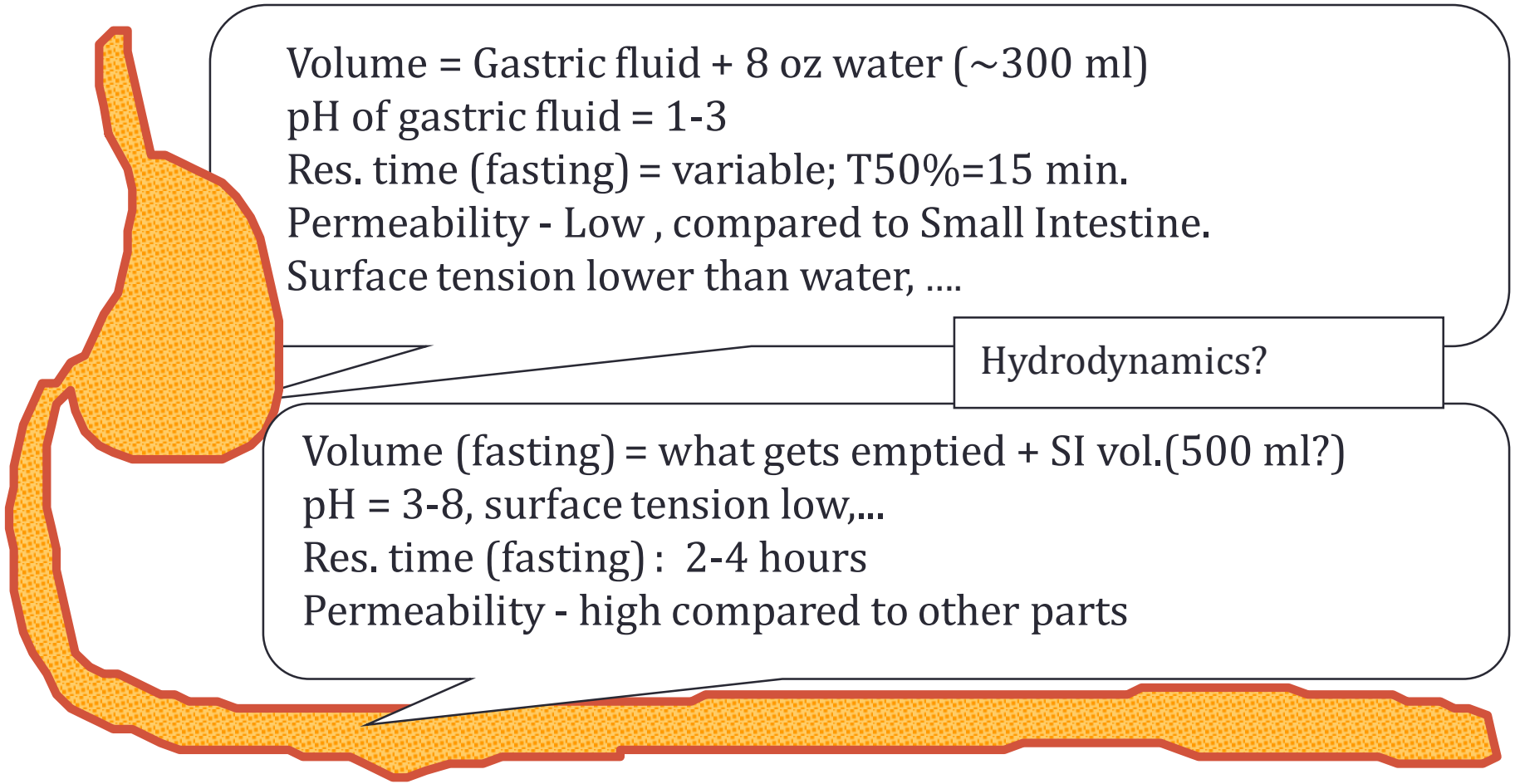
"Formulation Specific" IVIVC



Dissolution Test & Bioequivalence: Risk Assessment



Typical Physiologic Parameters:
Single Dose Fasting BE Study



When you change the way you look at a thing….

The paradigm shifts

http://www.fda.gov/ohrms/dockets/ac/04/slides/2004-4078S2_10_Amidon_files/frame.htm

- $M(t) = \iiint_0^t PC(\frac{dA}{dt})$
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Journal of Clinical Pharmacology, 2002;42:620-643

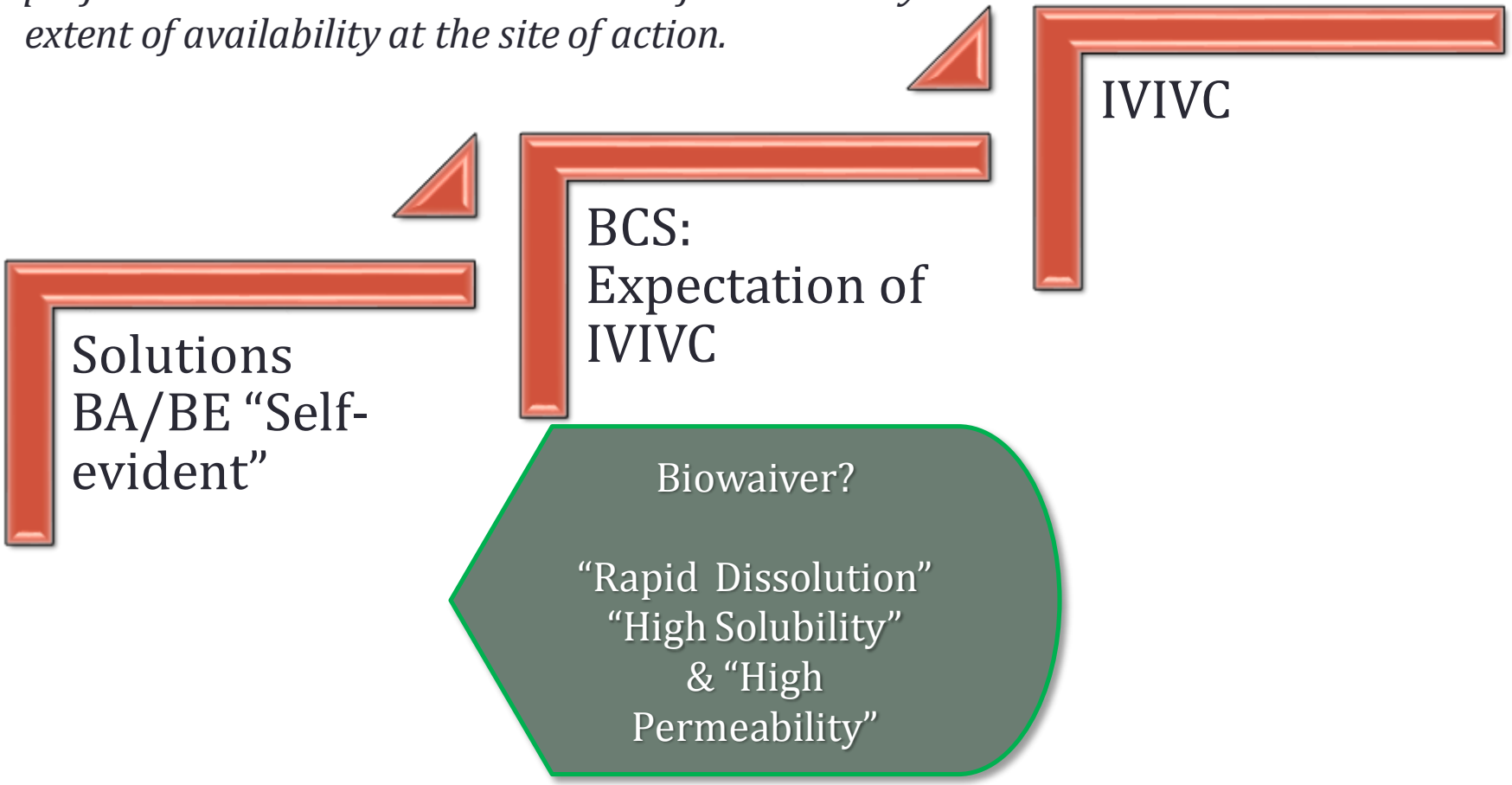
SUPAC-IR/BCS: For some 'Level 2' Changes

	HS/HP	*LS/HP*	*HS/LP*	*LS/LP*
Critical Process	Gastric Emptying	Dissolution	Permeability	D/P
IVIVC	Not likely	Likely	Not likely	(?)
Method	0.1 N HCl	pH 1 - 7.4	App/Comp	In Vivo BE
Acceptance Criteria	Single point 85% in 15 min	Multiple profiles (f2 > or = 50)	Single profile (f2 > or = 50)	AUC & Cmax 90% CI 80-125%

Note: NTI drugs excluded for some Level 2 Changes

Criteria for Biowaiver, New Applications?

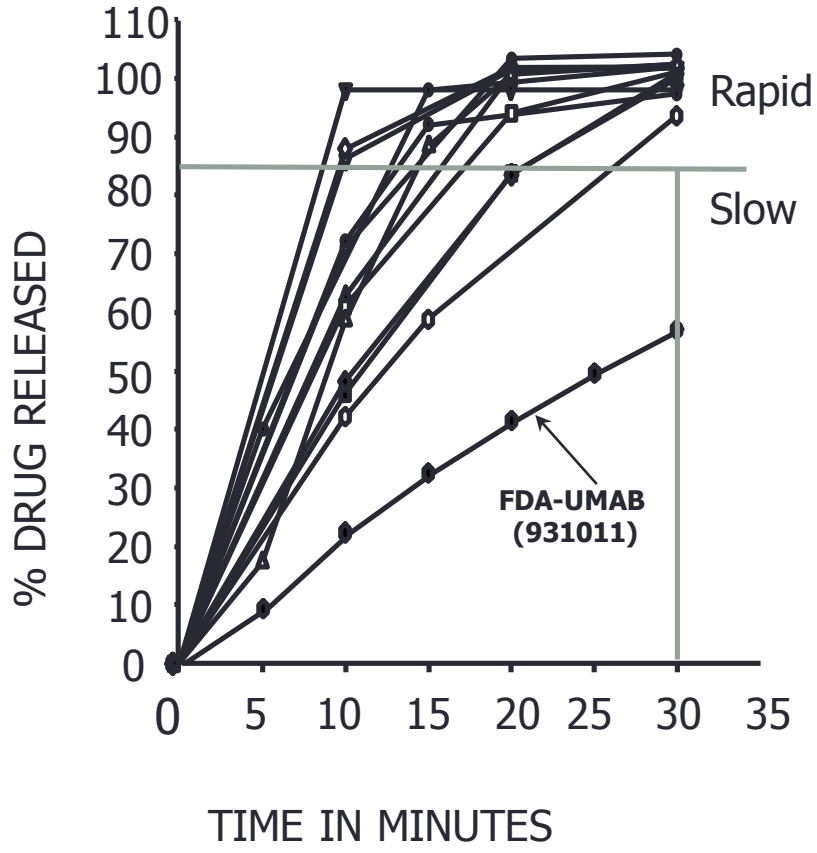
If two drug products, containing the same drug, have the same concentration time profile at the intestinal membrane surface then they will have the same rate and extent of availability at the site of action.

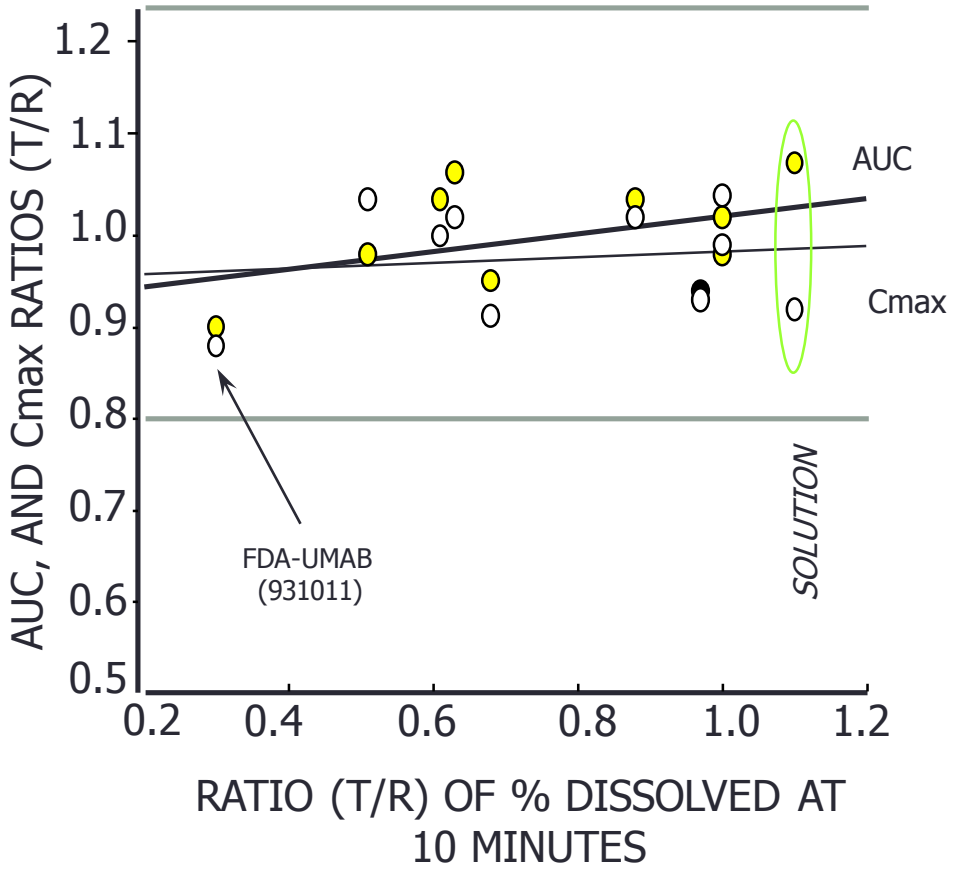


BCS: Class Membership

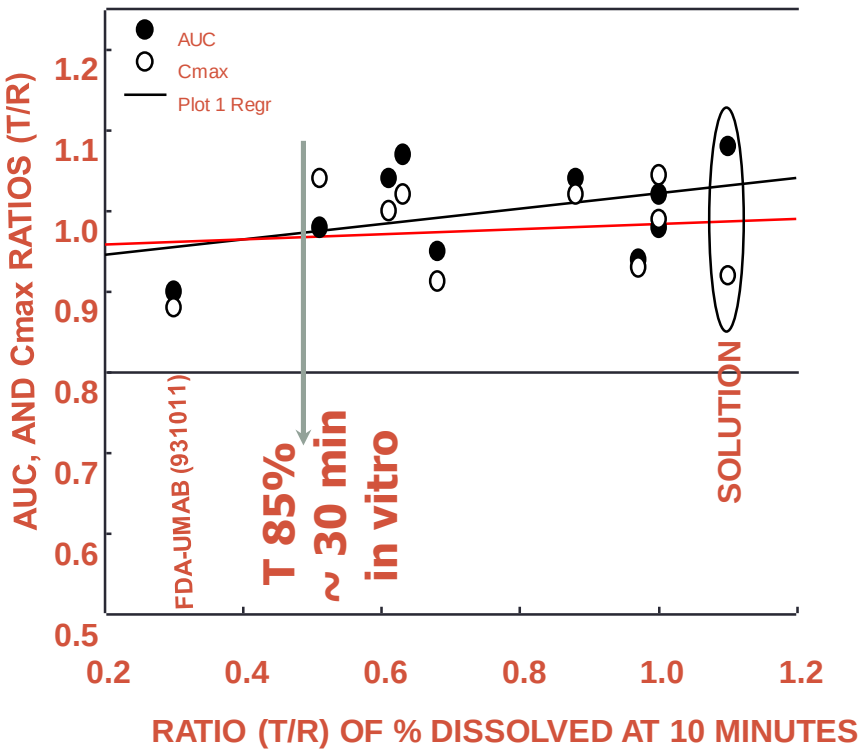
High Solubility	• the highest dose strength is soluble in ≤250 mL aqueous buffers over 1- 7.4 pH range of at 37°C.
High Permeability	• extent of absorption in humans is determined to be ≥ 90%
Rapid Dissolution	• ≥ 85% dissolves within 30 minutes in 0.1 HCl (or SGF), pH 4.5, and pH 6.8 buffers (or SIF) using Apparatus I at 100 rpm or Apparatus II at 50 rpm.

Metoprolol IR Tablets: In Vitro - In Vivo Relationship

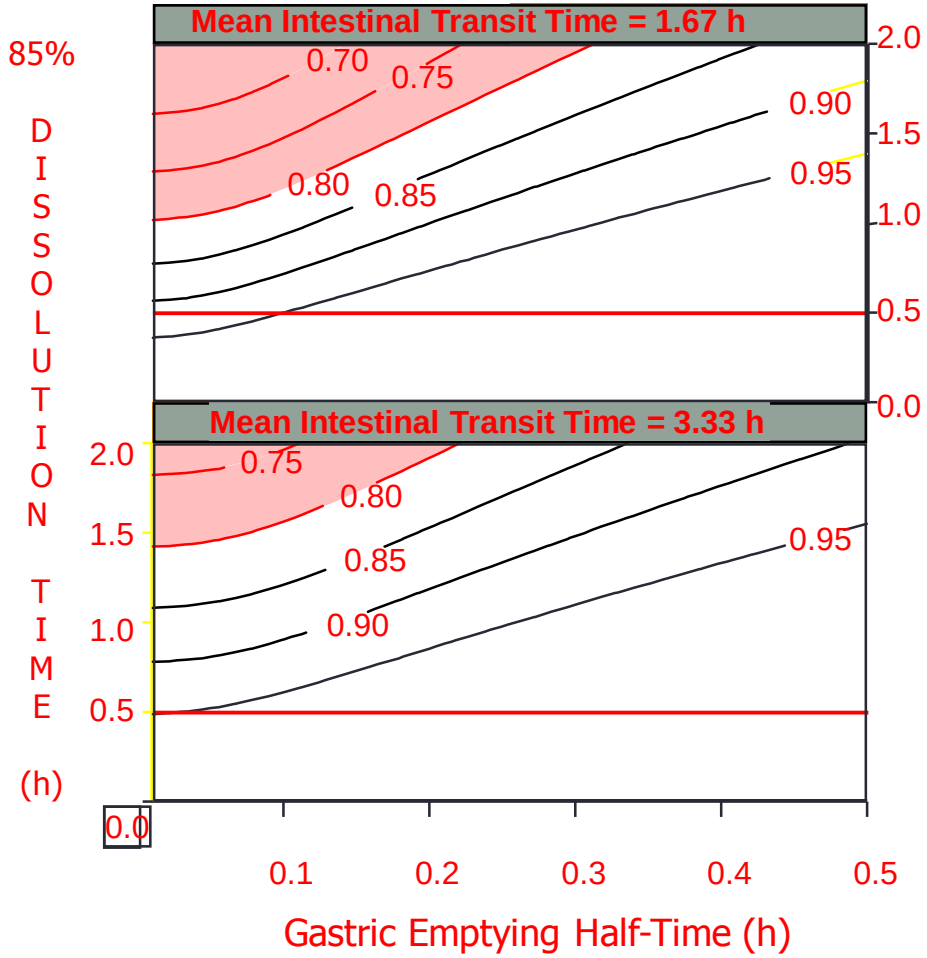




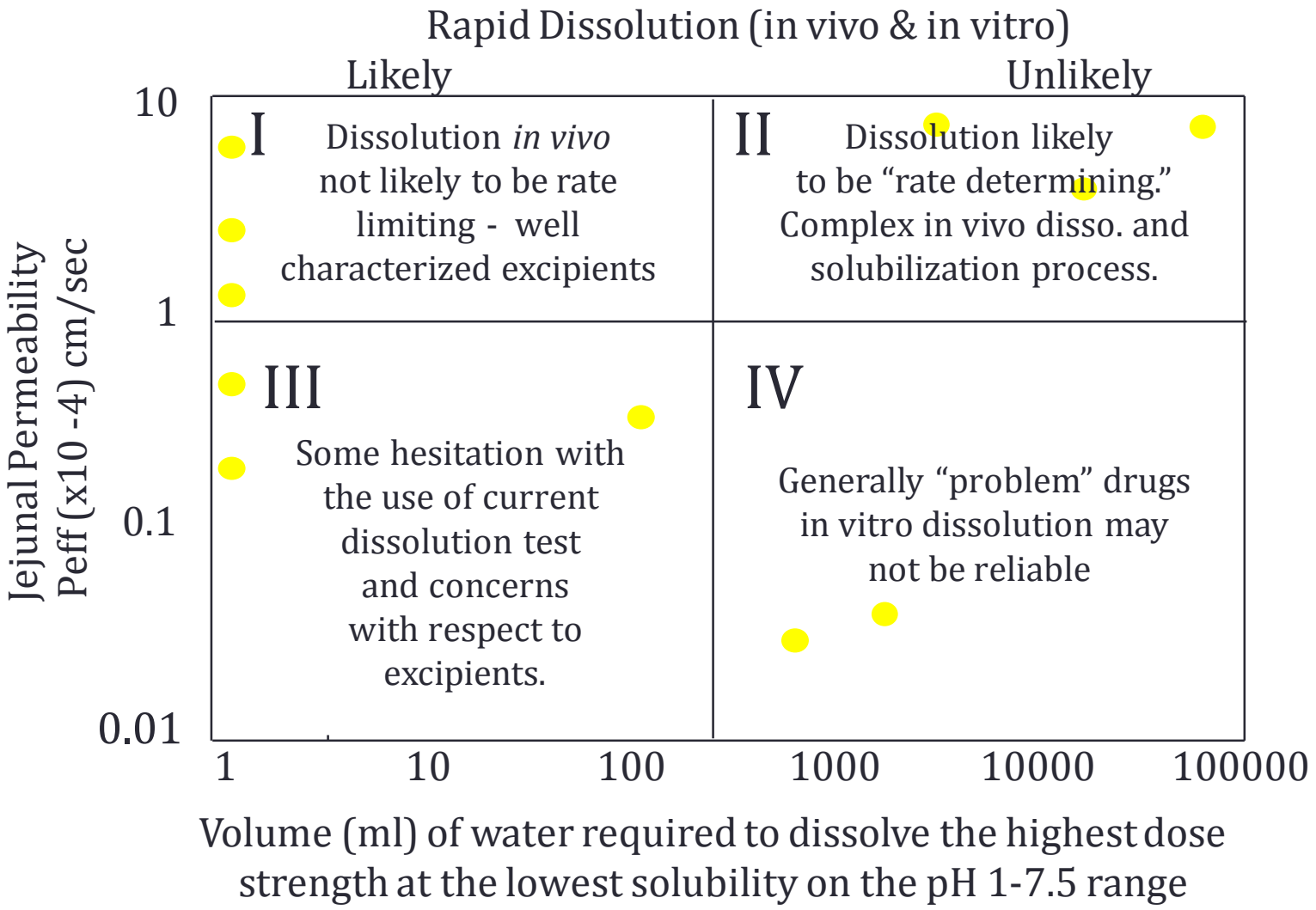
Metoprolol IR Tablets: Experimental & Simulation Data



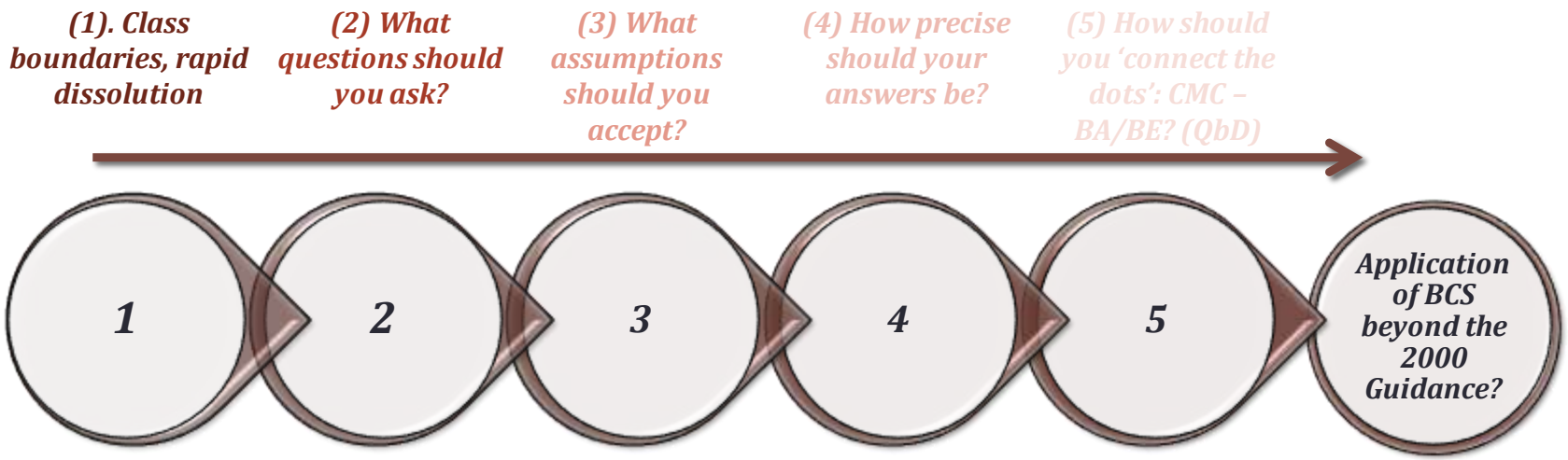
Kaus LC, Gillespie WR, Hussain AS, Amidon GL. *The effect of in vivo dissolution, gastric emptying rate and intestinal transit time on the peak concentration and area-under-the-curve of drugs with different gastrointestinal permeabilities.* Pharm. Res. ,16, 272 (1999)



BCS Class Membership: Risk Management

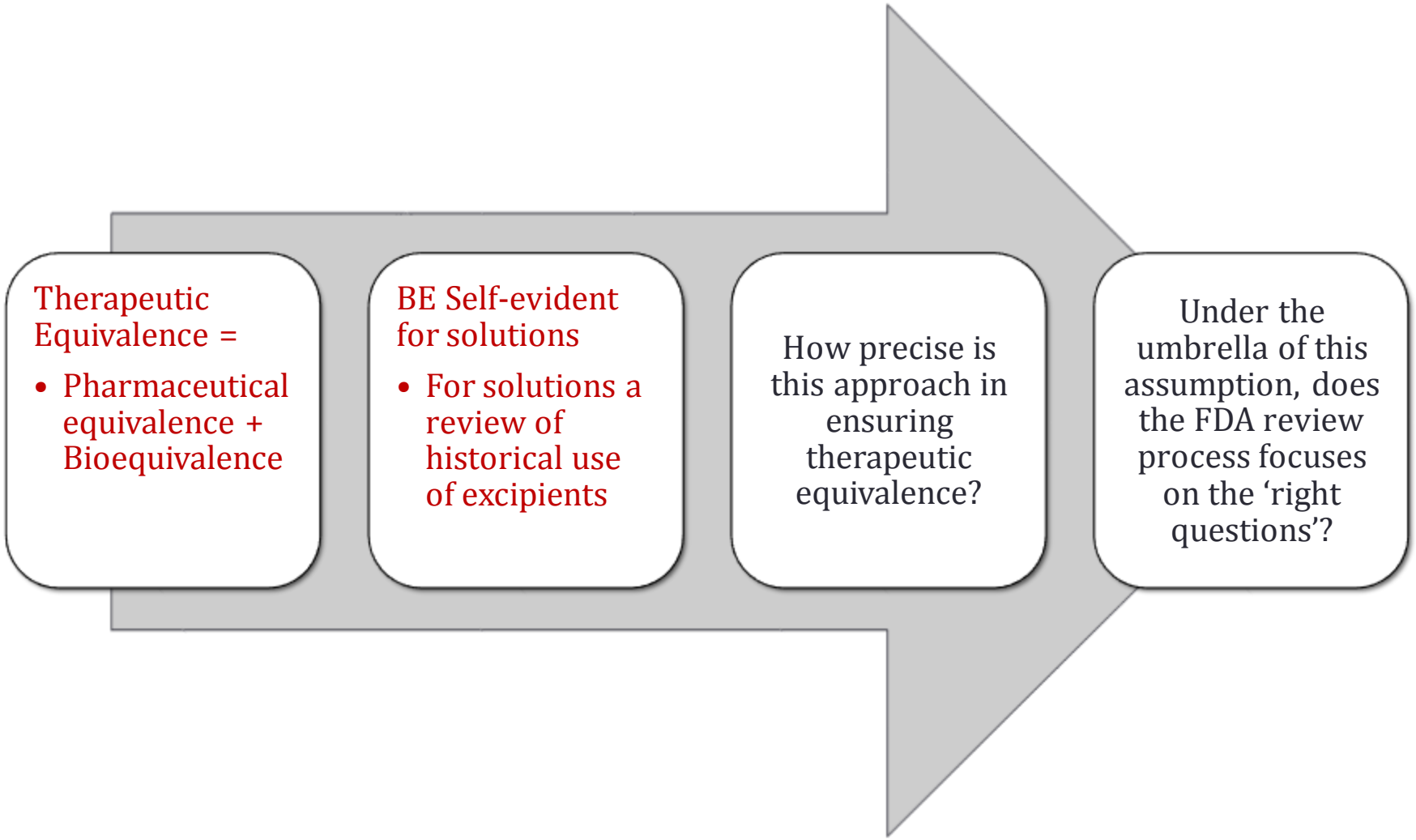


Re-cap and Next Steps



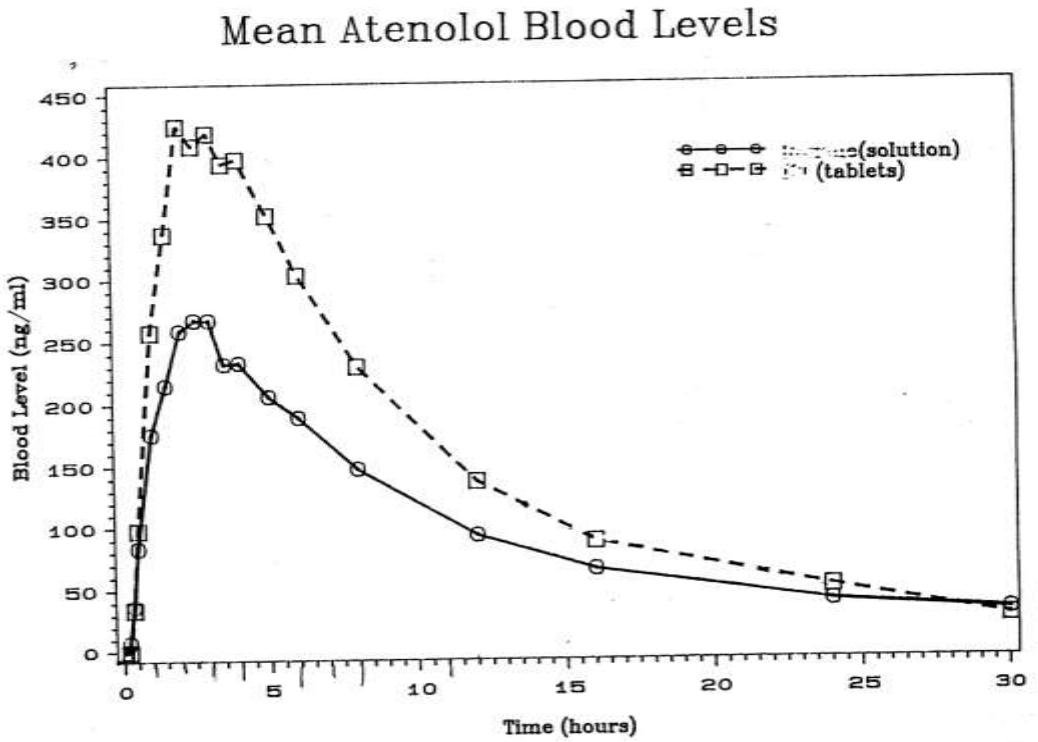
A successful application of BCS principles to a specific "locally acting" drugs (low to no permeability). FDA willing to make 'case-by-case' decision. Broad policy recommendation yet to be formulated.

Assumptions Acceptable to the Society?



Question: Why a tablet can exhibit higher bioavailability than a solution?

Note: Atenolol is a low permeability drug



www.fda.gov/ohrms/dockets/ac/05/.../2005-4137S2_02_Hussain.ppt

Experimental Formulation

	Reference	TEST formulation
Sucrose* (high permeability)	5 g	0 g
Sorbitol (low permeability)	0 g	5 g
Water	15 ml	15 ml
Drug 1	Ranitidine (low permeability)	
Drug 2	Metoprolol (high permeability)	

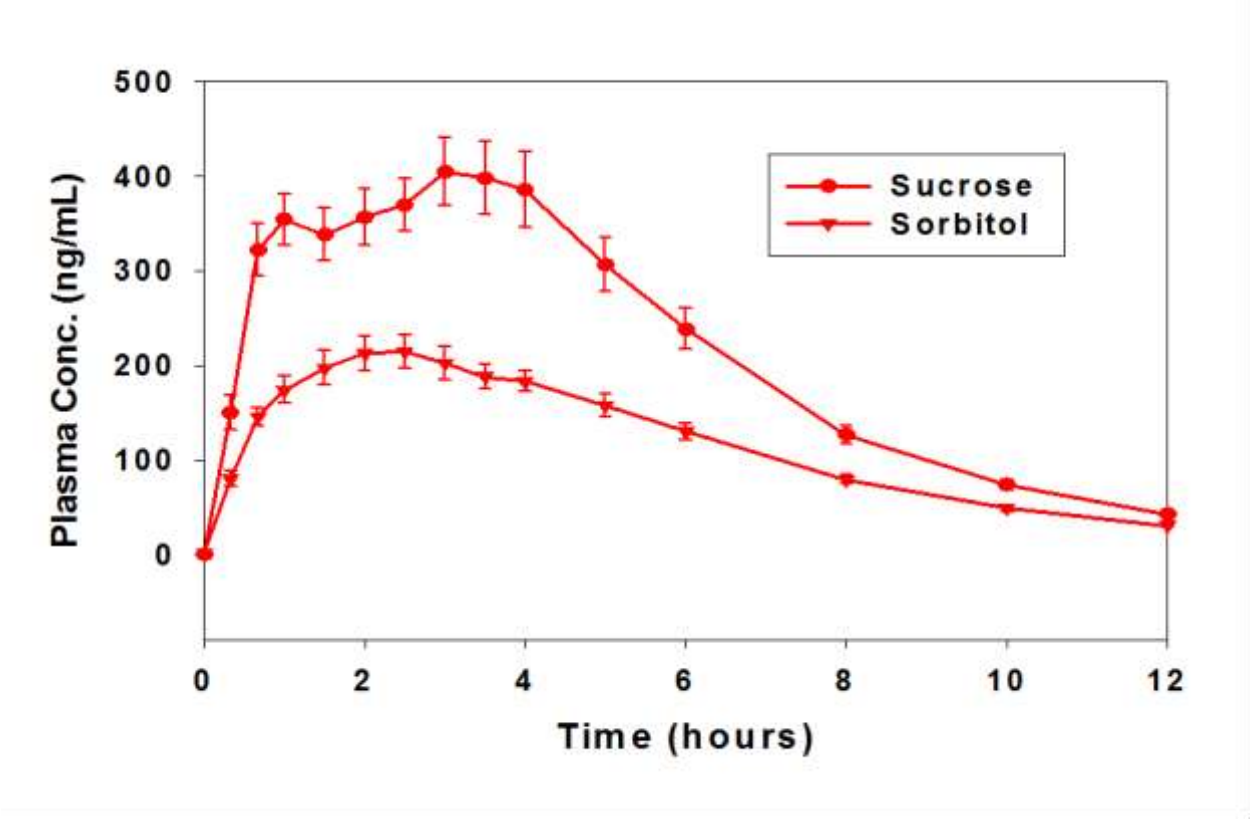
A Modern View of Excipient Effects on Bioequivalence: Case Study of Sorbitol

M.-L. Chen, A. B. Straughn, N. Sadrieh, M. Meyer, P. J. Faustino, A. B. Ciavarella, B. Meibohm, C. R. Yates and A. S. Hussain

Pharmaceutical Research, Volume 24, Number 1 (2007), 73-80, DOI: 10.1007/s11095-006-9120-4

* Rapidly metabolized at/in the intestinal wall to glucose and fructose, both exhibit complete absorption

Low permeability excipient can reduce bioavailability of a low permeability drug!



Ranitidine: 150 mg
Sucrose: 5 g
Sorbitol: 5 g

A Modern View of Excipient Effects on Bioequivalence: Case Study of Sorbitol
M.-L. Chen, A. B. Straughn, N. Sadrieh, M. Meyer, P. J. Faustino, A. B. Ciavarella, B. Meibohm, C. R. Yates and A. S. Hussain
Pharmaceutical Research, Volume 24, Number 1 (2007), 73-80, DOI: 10.1007/s11095-006-9120-4

Question: How do we select and evaluate the impact of excipients on BA/BE?

FDA's Inactive Ingredient Guide

- Has it been used previously?
- Many other issues
  - http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM291010.pdf

A logical extension – What gaps exist in the current definition of 'Pharmaceutical Equivalence"?

- A case example of micro-emulsion

Prescription for trouble*

How flaw in FDA safety net may pose risk to public with generic drugs

- Tom Abate, Todd Wallack, Chronicle Staff Writers
- San Francisco Chronicle. Sunday, December 22, 2002

The issues

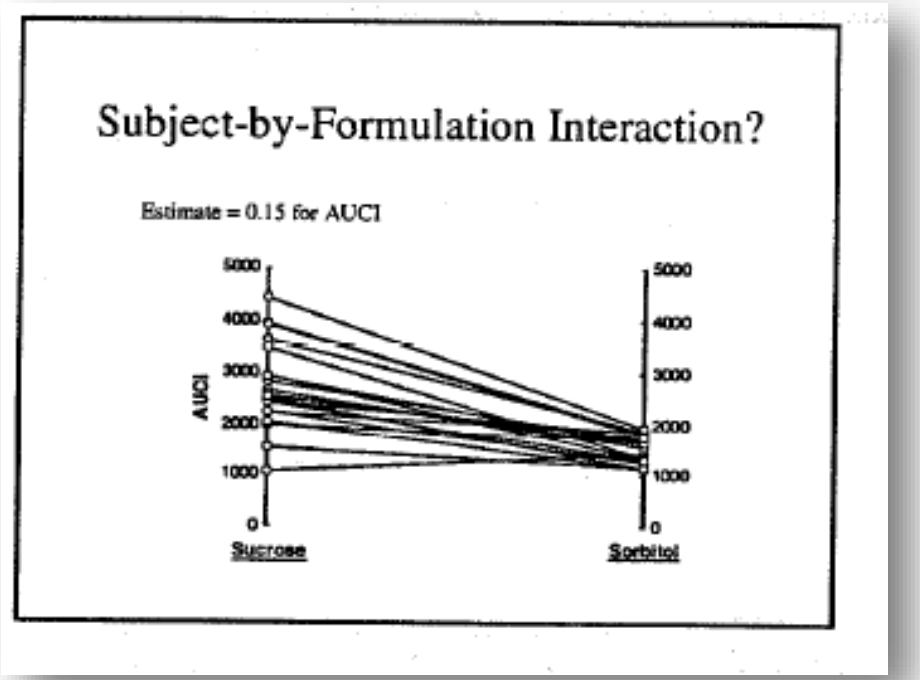
- *"[Company X] had tested its generic with chocolate milk. [Ref.product] was chased with apple juice."*
- *"Did that matter?"*

http://www.sfgate.com/cgi-bin/article.cgi?f=/c/a/2002/12/22/MN35888.DTL&ao=all

How precise should our answer be?

In parallel to development of BCS guidance the FDA had proposed replacing the "average bioequivalence" criterion with population and individual bioequivalence criteria

- To consider **variances in addition to the difference of averages.**
- One of these variances in the individual bioequivalence criterion measures **subject-by-formulation interaction**, the extent to which the test-reference difference varies from person to person.



Ranitidine AUC in individuals as a function of sucrose or sorbitol

http://www.fda.gov/ohrms/dockets/ac/00/slides/3657s2_07.pdf

Policy Recommendation: Waiver of *in vivo* BE studies based on BCS (8/30/2000)

Recommended for a solid oral Test product that exhibit ***rapid*** (85% in 30 min) and ***similar*** *in vitro* dissolution under specified conditions to an approved Reference product when the following conditions are satisfied:

- Products are ***pharmaceutical equivalent***
- Drug substance is ***highly soluble*** and ***highly permeable*** and is not considered have a ***narrow therapeutic range***
- Excipients used are not likely to effect drug absorption

BCS a tool for risk management (2000)

Assessment of risk	• What is the risk of bio-in-equivalence between two pharmaceutical equivalent products when *in vitro* dissolution test comparisons are used for regulatory decisions? • Likelihood of occurrence and the severity of the consequences?
Regulatory Decision	• whether or not the risks are such that the project can be persued with or without additional arrangements to mitigate the risk
Acceptability of the Decision	• is the decision acceptable to society?

Reliance on current dissolution practice can poses an unacceptable level of risk (2000)

Compared to high solubility drugs	Risk is higher for low solubility drugs
Products with slow or extended dissolution profiles pose a higher risk (dissolution rate limiting)	Need for a rapid dissolution criteria
Potential for differences between *in vivo* and *in vitro* "sink" conditions and impact of excipients	Higher for low permeability drugs

Re-cap (2000) & Update (Current state)

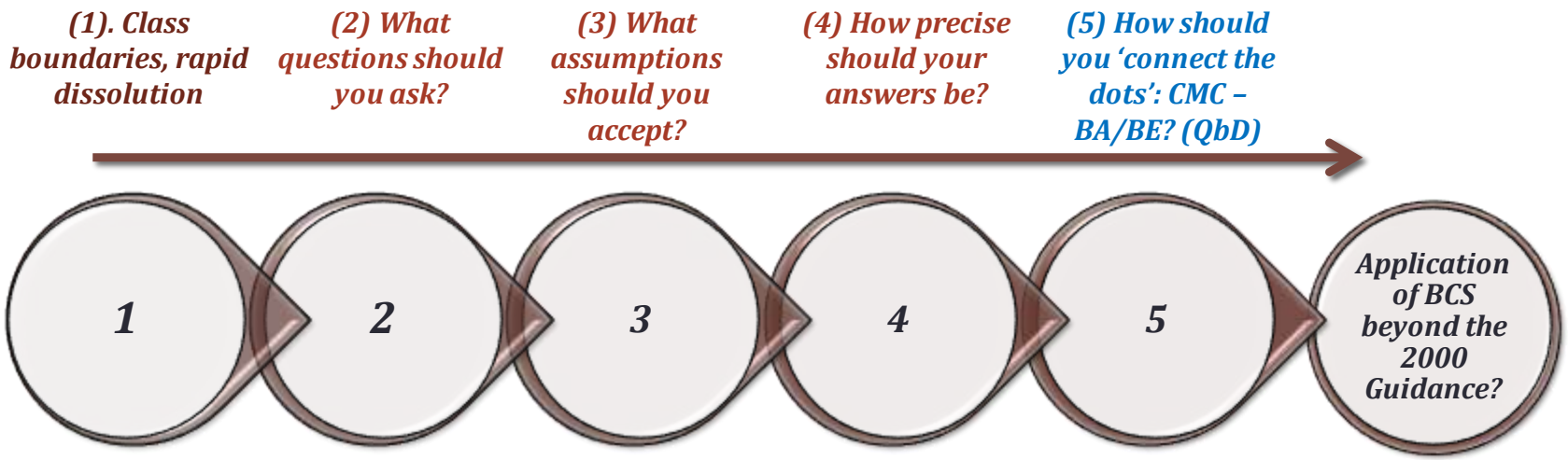
At the time the BCS guidance was being developed

- Focus on the "right question" during FDA review needed improvement
- Understanding of excipient*drug interactions was evolving
- Improved criteria for pharmaceutical equivalence assessment was needed
- Debate on "average bioequivalence", population and individual bioequivalence criteria

Following issuance of the BCS guidance

- FDA maintained "avg. BE" & launched the PAT/QbD program
- FDA-OGD adopted a "Question based Review" process to focus on the "right questions"
- OGD is now actively seeking to link QbD to Pharmaceutical Equivalence Assessment
- "Pharmaceutical equivalence by design for generic drugs: modified-release product" Pharm Res. 2011 Jul;28(7):1445-53

Re-cap and Next Steps



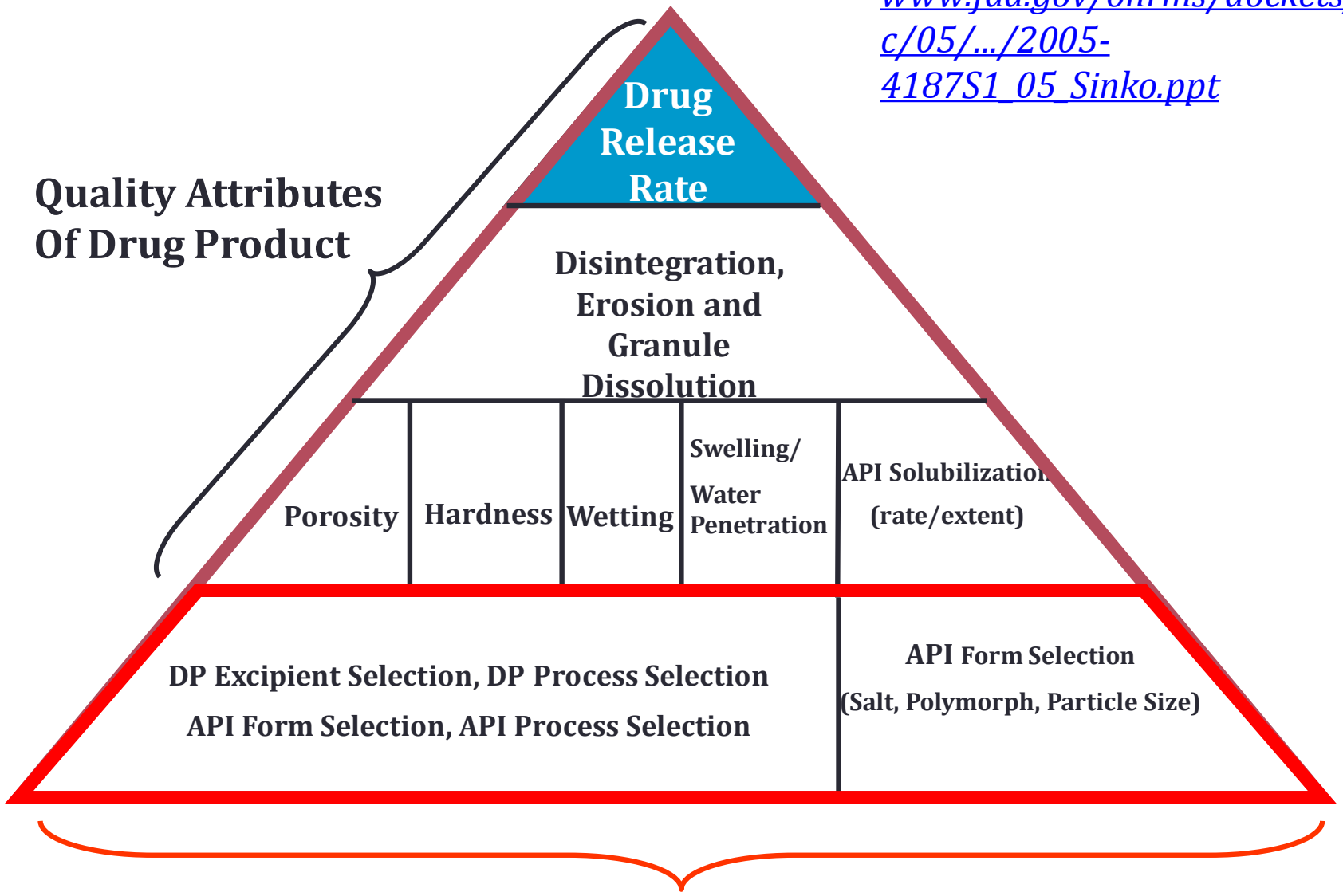
A successful application of BCS principles to a specific "locally acting" drugs (low to no permeability). FDA willing to make 'case-by-case' decision. Broad policy recommendation yet to be formulated.

Drug Release & Quality by Design

- Christopher Sinko, Ph.D., at the Advisory Committee for Pharmaceutical Science meeting, on October 25, 2005
  - *www.fda.gov/ohrms/dockets/ac/05/.../2005-4187S1_05_Sinko.ppt*
  - Clinical relevance of release and stability specifications
  - Correlation between process parameters and ability to achieve specifications (and therefore remain clinically relevant

- Once a formulation scientist understands the patient's requirements, they can design a formulation using either or both approaches:
  - Prior knowledge: choose API form, excipients and processes that will achieve the expected release profile
  - QBD: select API form, excipients and processes that have greatest impact on quality attributes that affect release of drug
    - Selections based on theoretical/fundamental understanding, alternative measurements and heuristic development

www.fda.gov/ohrms/dockets/ac/05/.../2005-4187S1_05_Sinko.ppt

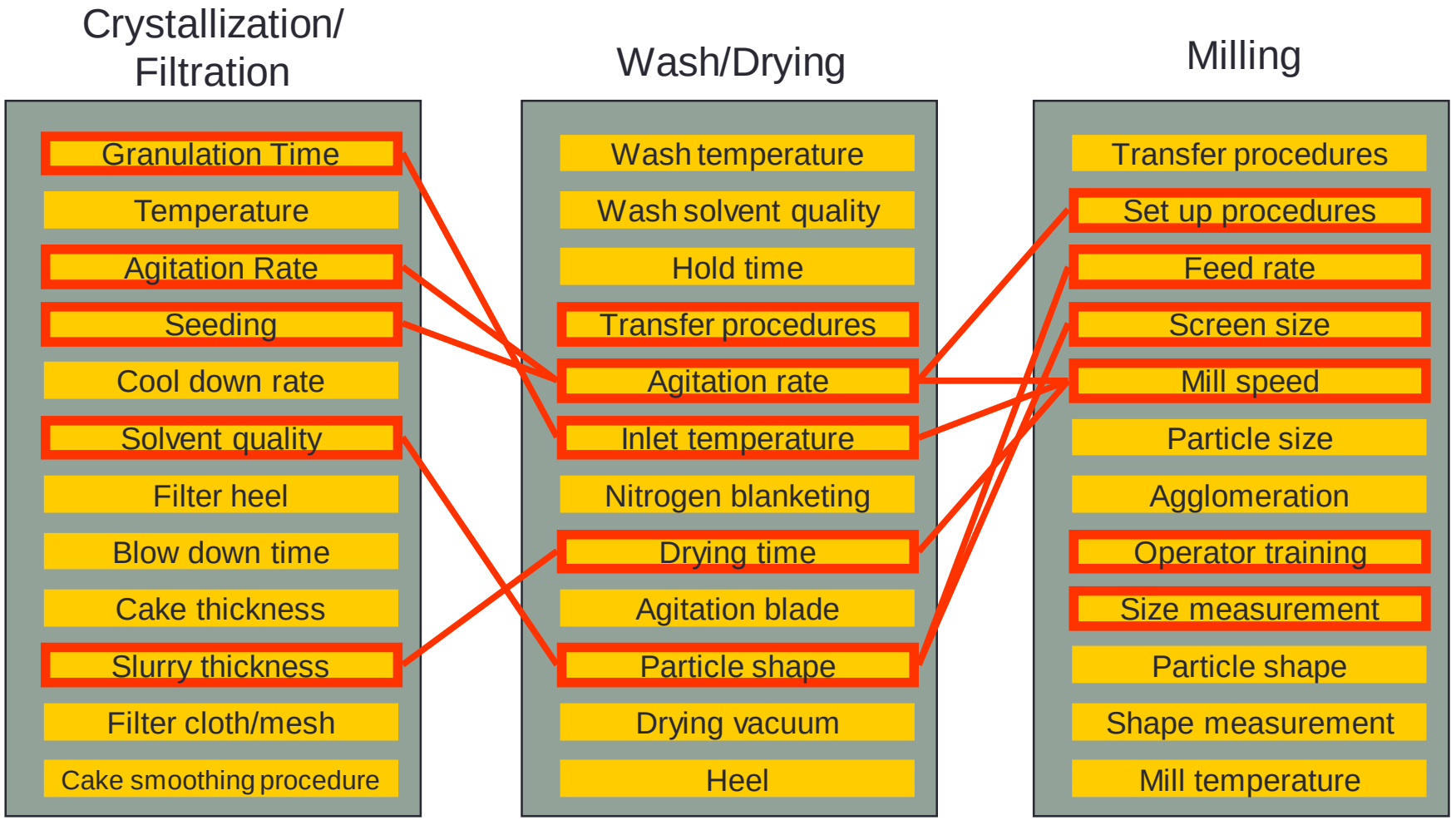


Features of "Quality by Design": doing things consciously*

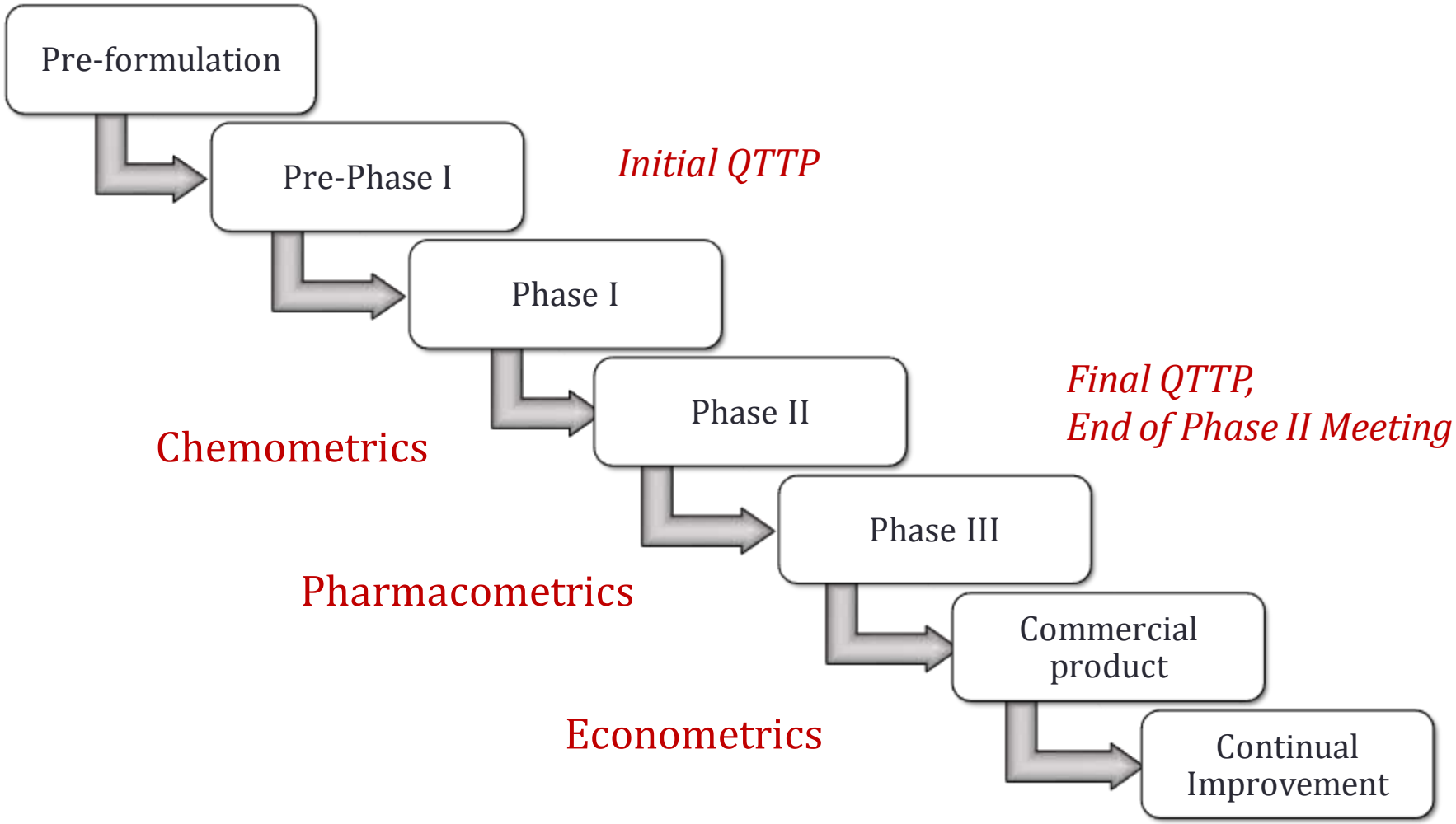
*A Quality by Design Approach to Dissolution Based on the Biopharmaceutical Classification System, R. Reed

Design Space: *API Particle Size*

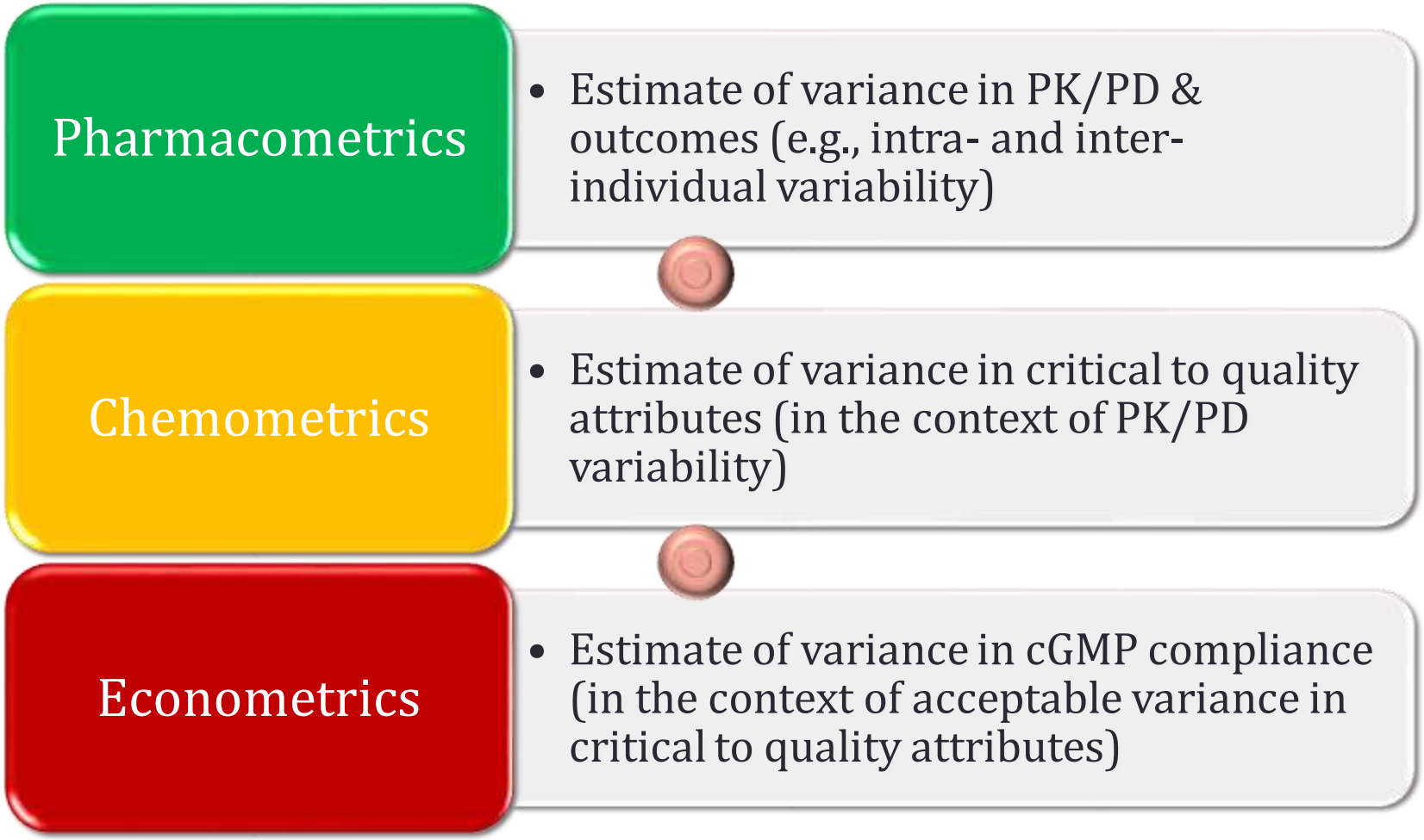
www.fda.gov/ohrms/dockets/ac/05/.../2005-4187S1_05_Sinko.ppt



Chemometrics, Pharmacometrics and Econometrics: Three Dimensions of QbD



Opportunities; only when the disciplinary divides are bridged

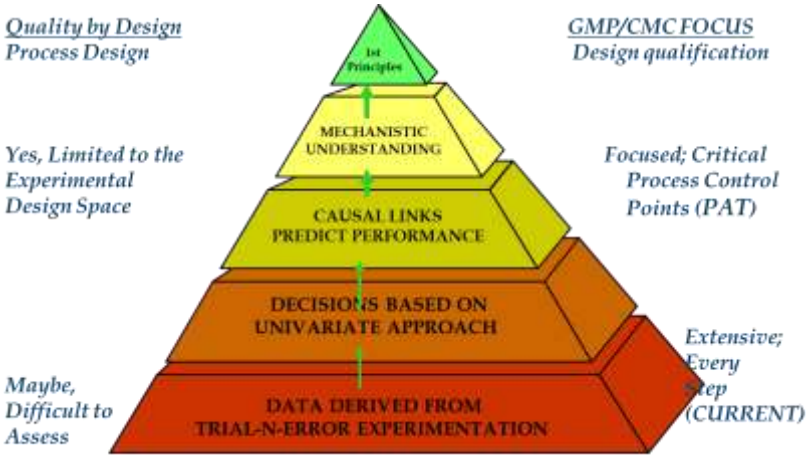


A vision becoming reality….

"I can see clearly now"
Vision 2020

- Perspectives on Regulation: Law, Discretion, and Bureaucratic Behavior (Kagan and Scholz, May 1980)
  - 'Good citizens' Vs. {'political citizens, 'incompetent', and/or 'amoral'}
- For FDA to be science and risk-based it needs scientific data & information, capability, ..

"Scientific explanation yields understanding"



http://www.fda.gov/ohrms/dockets/ac/04/briefing/2004-4052B1_09_Hussain-Arden-UK-Presentation.ppt

Learning objectives

Broadly, gain an understanding of considerations in translating scientific knowledge into regulatory policy

(1). Considerations for developing the FDA guidance
"Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System" (August 2000)

Develop a basis to critically evaluate considerations utilized for development of the FDA guidance document

(2) What questions should you ask?

(3) What assumptions should you accept?

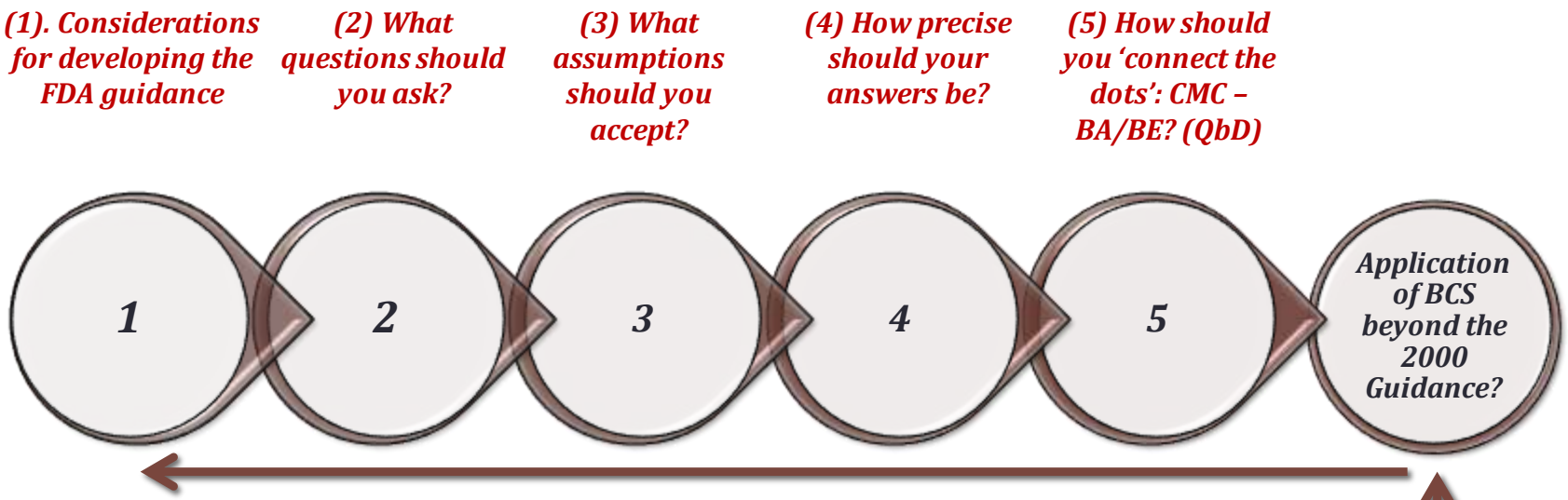
(4) How precise should your answers be?

Identify and explain how future regulatory applications of BCS may be realized in the context of 'Quality by Design'

(5) How should you 'connect the dots': CMC – BA/BE?

Can you justify new applications of BCS (i.e., beyond the 2000 guidance)?

Presentation Summary



VIROPHARMA INCORPORATED, Plaintiff,
Vs.
MARGARET A. HAMBURG, M.D., et al., Defendants.

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA
Civil Action No. 12-cv-00584-ESH
Filed 04/17/12