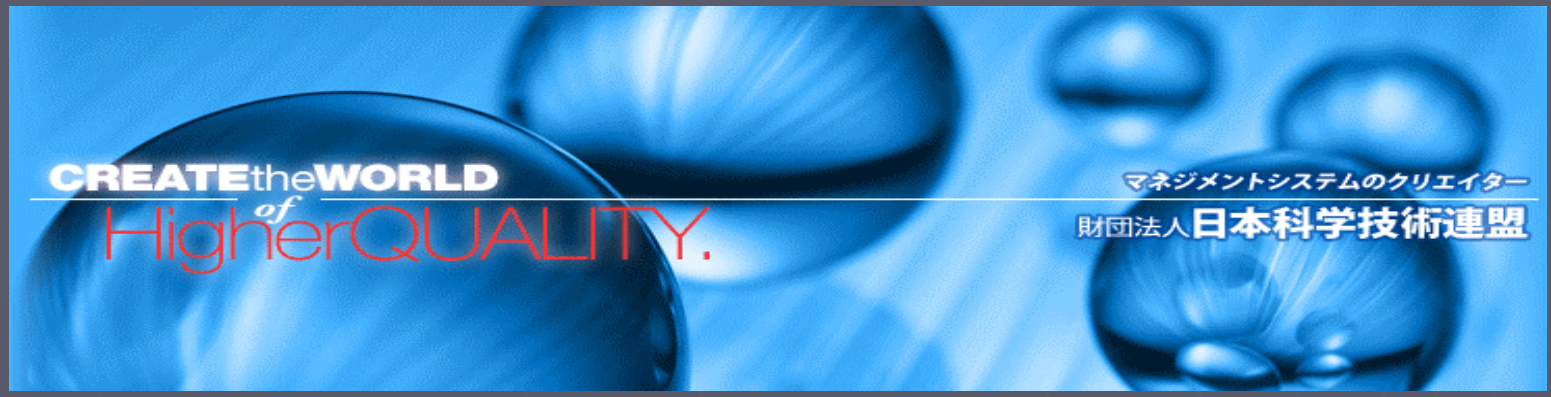
Effective Regulatory System: Importance of Process Understanding and Quality by Design

Ajaz S. Hussain, Ph.D.
Office of Pharmaceutical Science
Center for Drug Evaluation and Research
Food and Drug Administration

Pharmaceutical Quality Forum: 3rd Symposium
November 2004, Tokyo, Japan



TQM is a set of systematic activities carried out by the entire organization to effectively and efficiently achieve company objectives so as to provide products and services with a level of quality that satisfies customers, at the appropriate time and price.

"Quality" refers to usefulness (both functional and psychological), reliability and safety. Also in defining quality, influence on the third parties, society, the environment and future generations must be considered.

"Customers" include buyers but also users, consumers and beneficiaries.

日本科学技術連盟
Union of Japanese Scientists and Engineers

http://www.juse.or.jp/e/deming/prizelist2004.html

2004 Deming Prize

- **The Japan Quality Medal**
  - GC Corporation (Japan)
- **The Deming Prize for Individuals**
  - Mr. Akira Takahashi, Senior Adviser to the Board, Denso Corporation (Japan)
- **The Deming Application Prize (alphabetical order)**
  - CCC Polyolefins Company Limited (Thailand)
  - Indo Gulf Fertilisers Limited (India)
  - Lucas-TVS Limited (India)
  - Siam Mitsui PTA Company Limited (Thailand)
  - SRF Limited, Industrial Synthetics Business (India)
  - Thai Ceramic Company Limited (Thailand)
- **The Nikkei QC Literature Prize (Available in Japanese only)**
  - *The First Book of the Taguchi Method* , Mr. Kazuo Tatebayashi, JUSE Press Limited
  - *Breakthrough Management* , Dr. Shoji Shiba, Toyo Keizai Inc.

日本科学技術連盟
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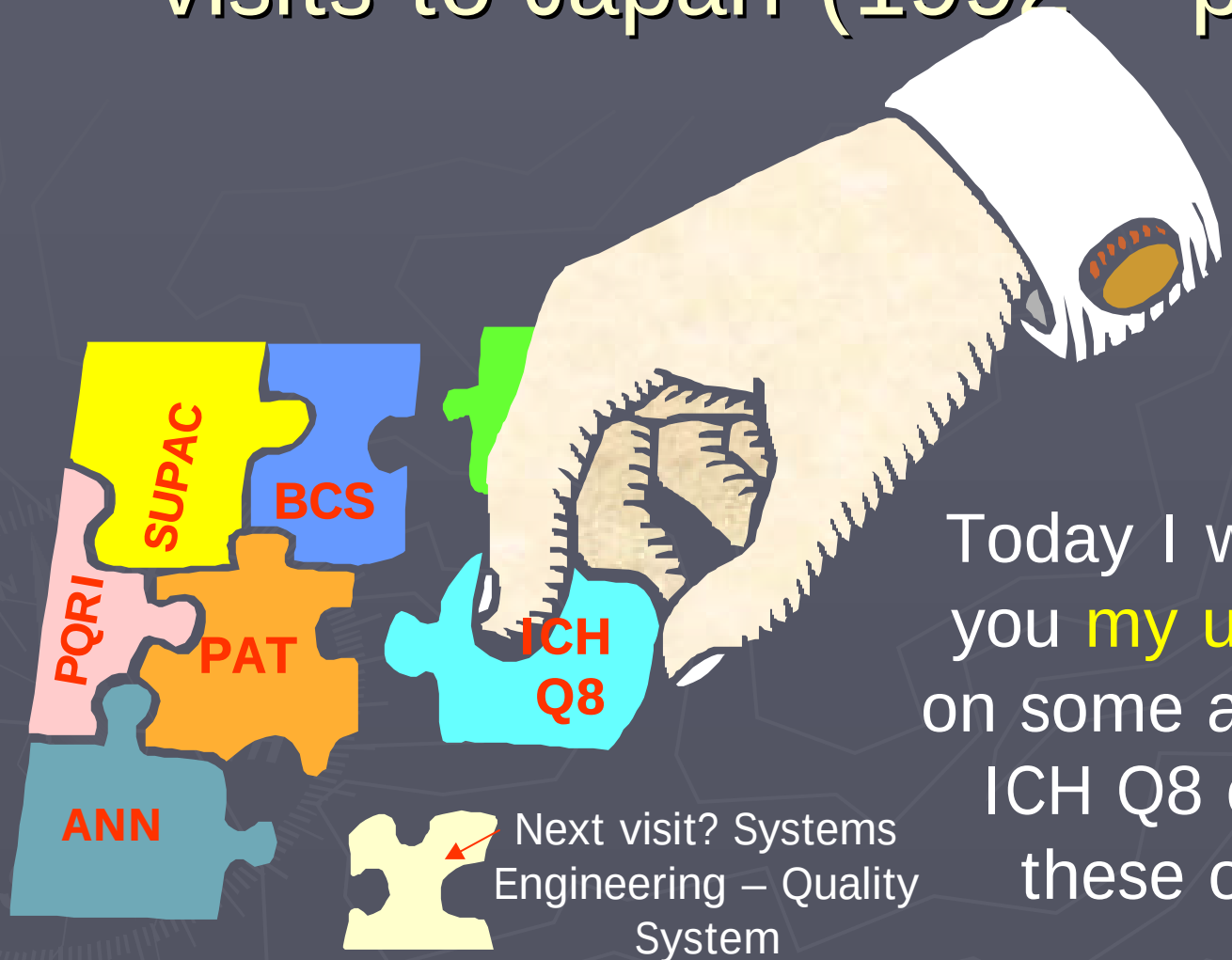
http://www.juse.or.jp/e/deming/prizelist2004.html

Key Presentation Topics: Previous visits to Japan (1992 – present)



Next visit? Systems Engineering – Quality System
and the role of ASTM

Today I will share with you my understanding on some aspects of how ICH Q8 can relate to these other topics

FDA/ISPE Forum on New PAT Guidance
8 December 2004, Yurakucho Asahi Hall
Tokyo, Japan

FDA /ISPE共催

Process Analytical Technology (PAT) Forum

新製薬技術への挑戦–21 世紀はさらにサイエンスベースへ

（同時通訳つき）

講演会とパネルデスカッションで

FDA との直接対話に参加しませんか！

セミナーは先着 600 名で締切ります。（締切りは 12 月 1 日）

協賛：医薬品品質フォーラム、製剤機械技術研究会、日本ＰＤＡ

後援：厚生労働省（予定）

開催日：12 月 8 日（水）午前 10 時開場午前 10 時半開演 - 午後 5 時終了

会場　：有楽町朝日ホール（JR 山手線　有楽町駅前、マリオン１１階）

Office of Pharmaceutical Science (OPS), CDER, FDA

- Responsible for the functions of
  - Office of Generic Drugs
  - Office of New Drug Chemistry
  - Office of Biotechnology Products
  - Office of Testing & Research
- Protecting and advancing public health
  - High quality drugs
  - Secure supply
  - Affordable drugs
  - Speed Innovation
  - Public confidence

Focus on improving "process understanding & quality by design"

San Francisco Chronicle

Prescription for trouble
How flaw in FDA safety net may pose risk to public with generic drugs
Sunday, December 22, 2002

Tom Abate, Todd Wallack, Chronicle Staff Writers

FDA castigated over generic drug loophole

Tuesday, December 24, 2002

LETTERS TO THE EDITOR

Wednesday, December 25, 2002

IN THE DARK AT FDA

JOHN BUFFUM
Pharmacy Planning Services, Inc.
Assoc. clinical professor of pharmacy
UCSF San Francisco

Assuring Quality by Design

- Provides a higher level of assurance than only “testing to document quality”
  - Remember the simple illustrations of this concept by Deming!
- Currently our regulatory system is leaning more towards “testing to document quality”
  - Need to strengthen our quality foundation
- It is a “Win-Win-Win” approach!

Patient Company Society

Deterministic interpretation: Specification - to - Performance

- "When tested *in vivo* – products that meet specification are bioequivalent (BE) and those failing specification are not BE"
- Due to random variation, the deterministic interpretation is not appropriate – conditional probability
- A strong argument for QbD

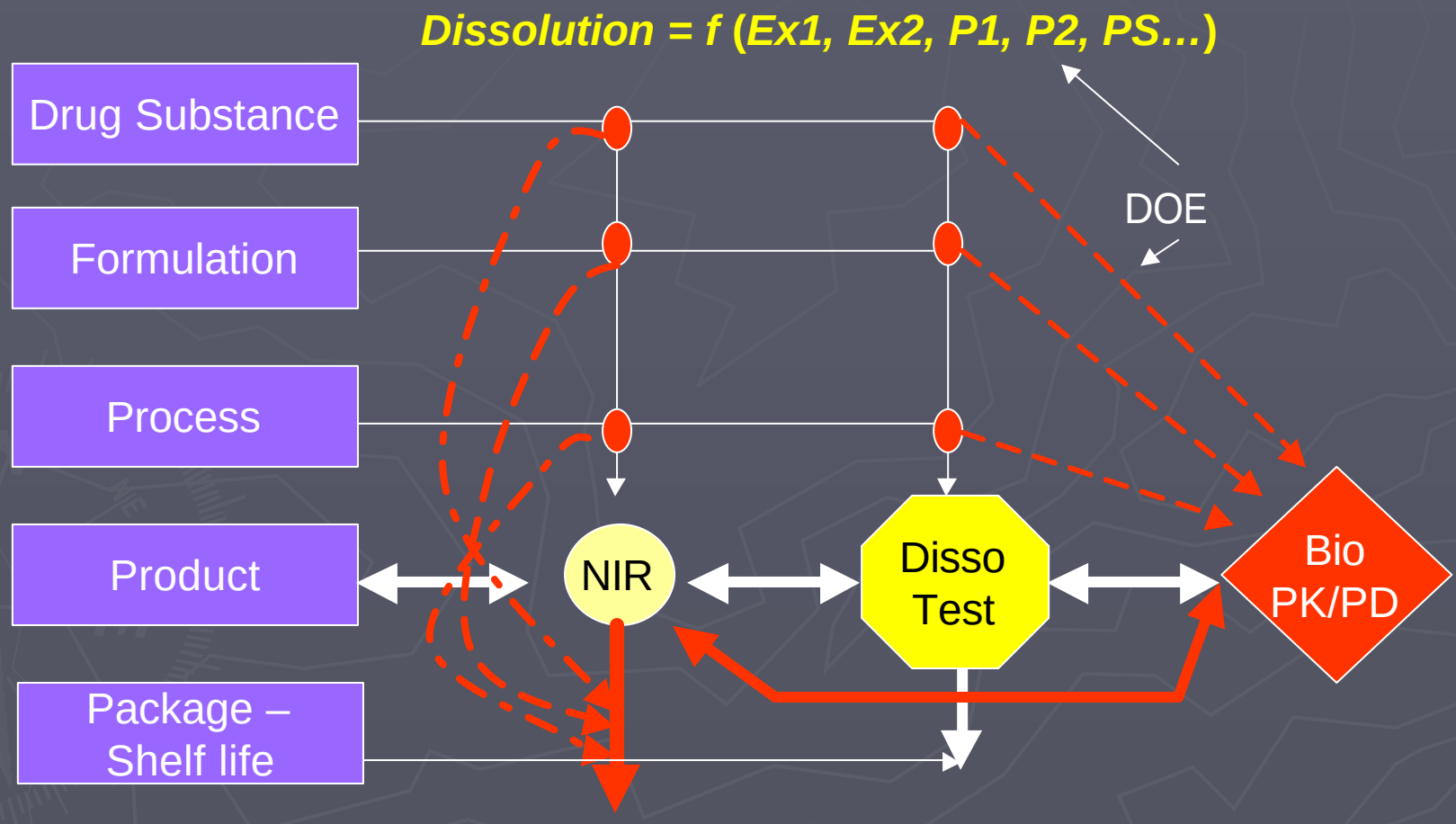
Table 7. Results of the Simulation Experiment, Showing the Number of Batches Belonging to Each of the Four Possible Categories

	Bioequivalence	
Dissolution Test	Passed	Failed
Passed	1483	1260
Failed	653	5604

JOURNAL OF PHARMACEUTICAL SCIENCES, VOL. 93, NO. 3, MARCH 2004

S. Hayes, A. Dunne, T. Smart, J. Davis. Interpretation and optimization of the dissolution specifications for a modified release product with an in vivo-in vitro correlation (IVIVC). J.Pharm.Sci. 93:571-581 (2004)

Controlling Dissolution: Conceptual Illustration



Control &“Real Time” Release

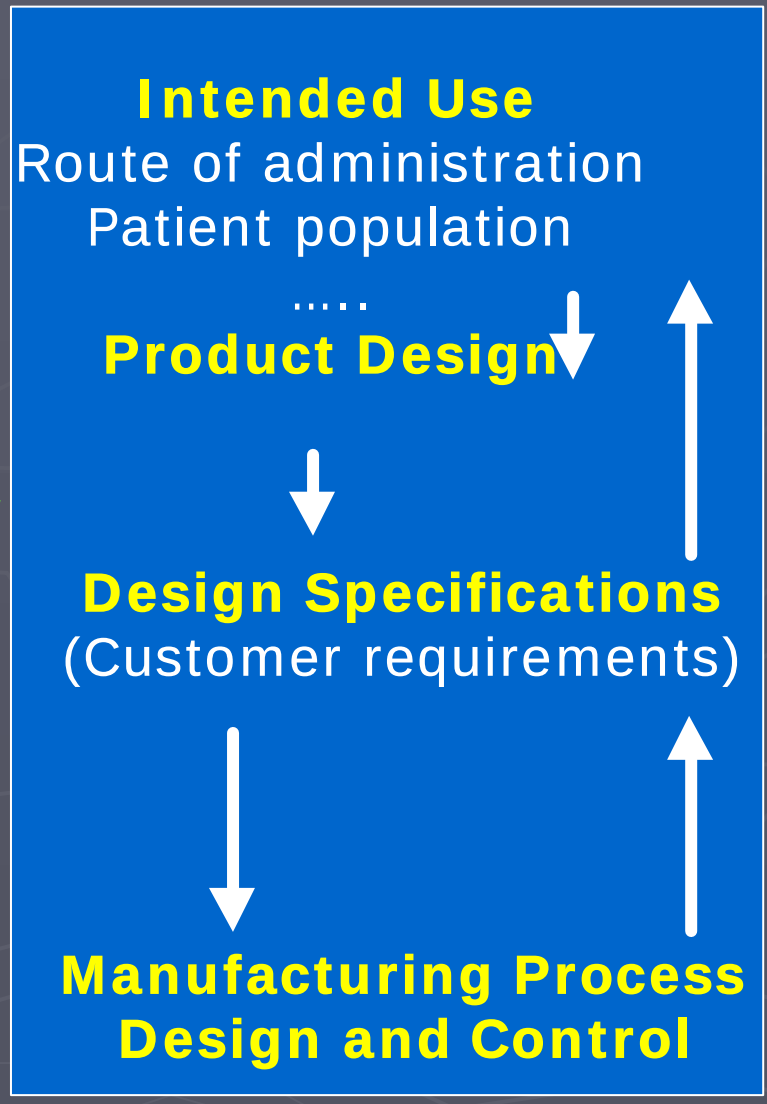
Quality by Design & Well Understood Product and Processes

- Methods to solve complex multi-factorial problems
  - DOE such as Taguchi's designs
- New measurement, control and information technologies
  - Predict, control and assure quality & performance
- Fundamental science and engineering principles
  - Knowledge based

→

- All critical sources of variability are identified and explained
- Variability is controlled by the process
- Product quality attributes can be accurately and reliably predicted over the design space established for materials used, process parameters, environmental and other conditions

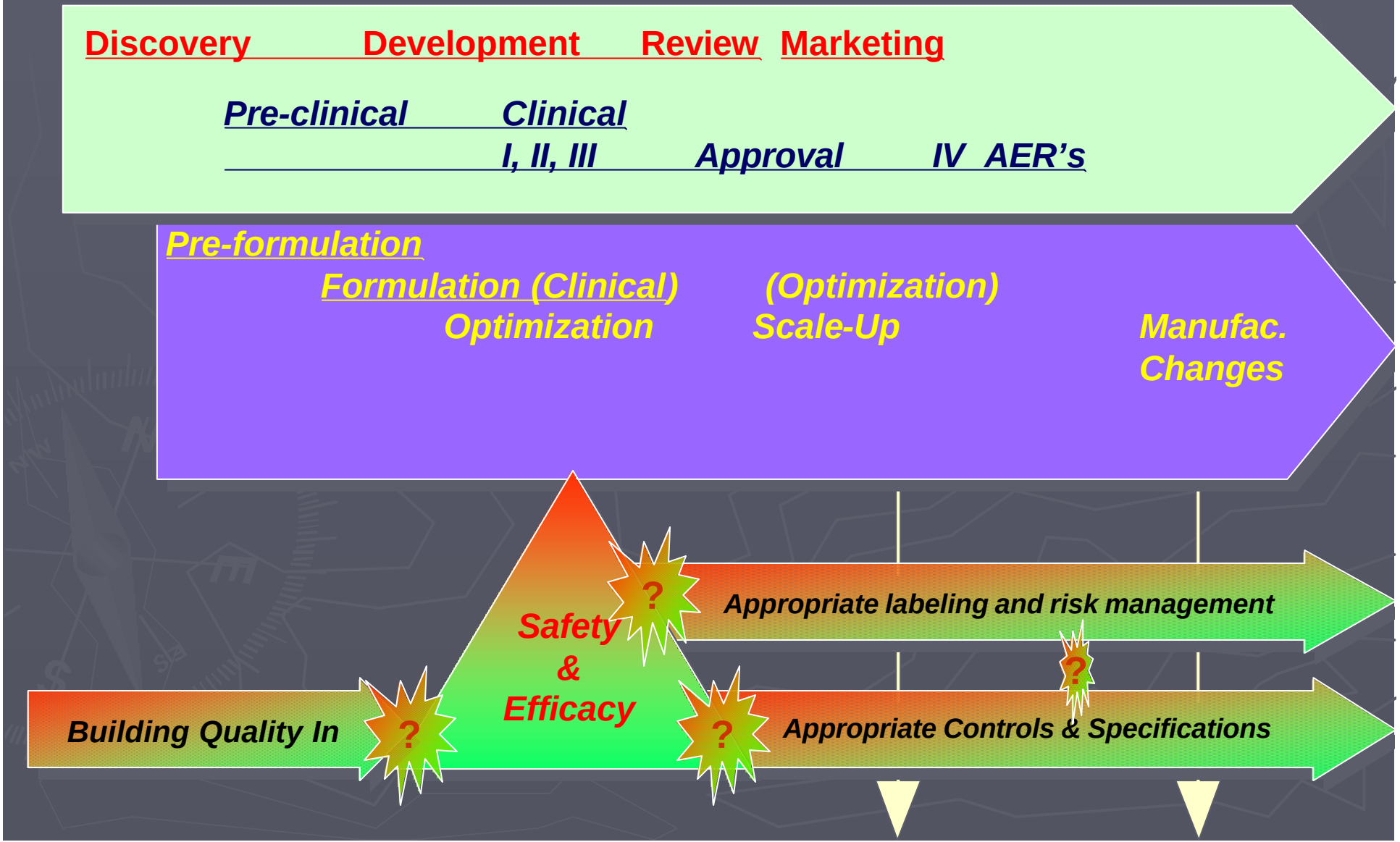
Design is about doing things consciously



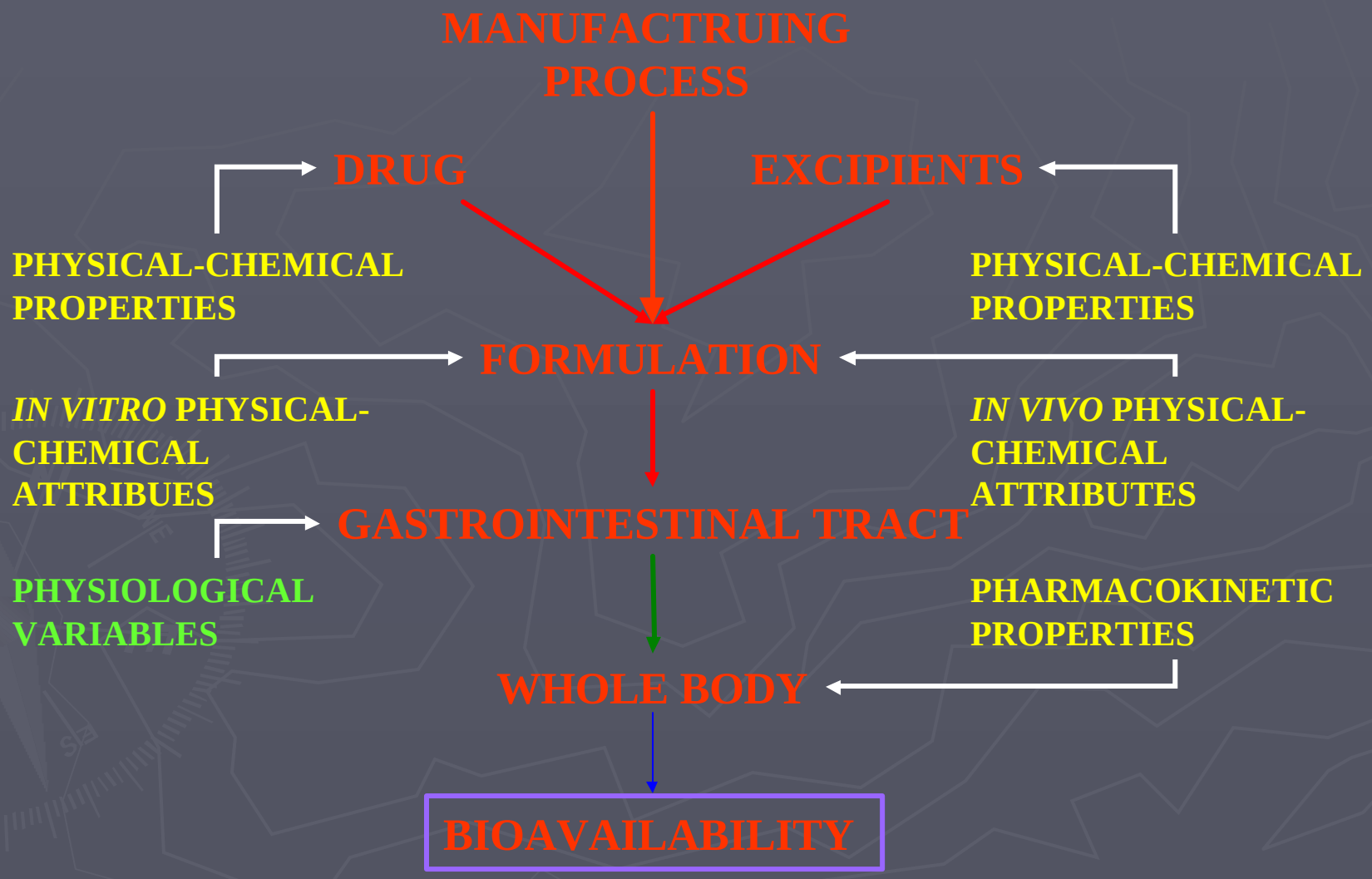
Product Performance:
Design specifications reliably and consistently deliver the therapeutic objectives

Capability
Ability to reliably and consistently deliver the target product design specifications

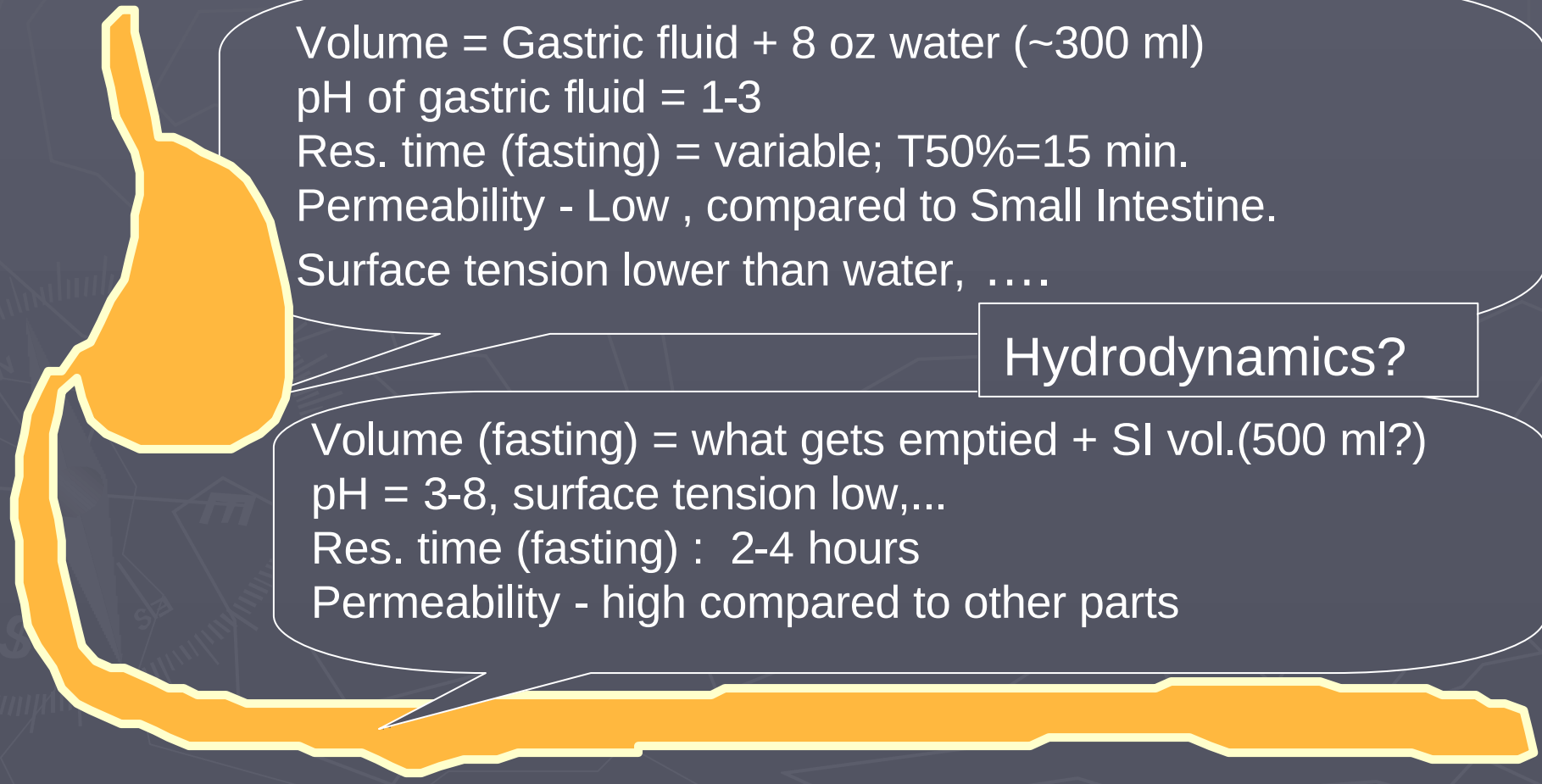
Systems Approach: Integration across disciplines, organization, and over time



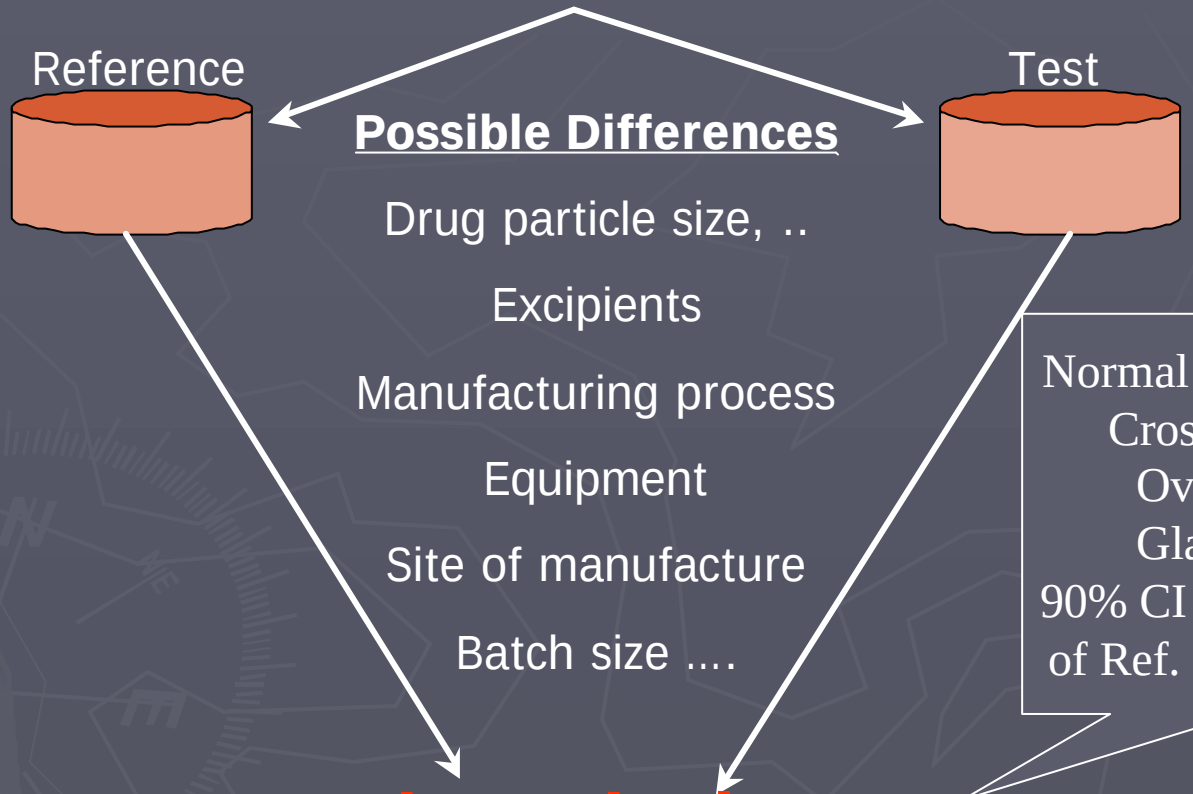
Elements of QbD (Example) – Bioavailability: Rapid and Complete Absorption & Reproducible



Typical Physiologic Parameters:
Single Dose Fasting BE Study



Pharmaceutical Equivalent IR Products



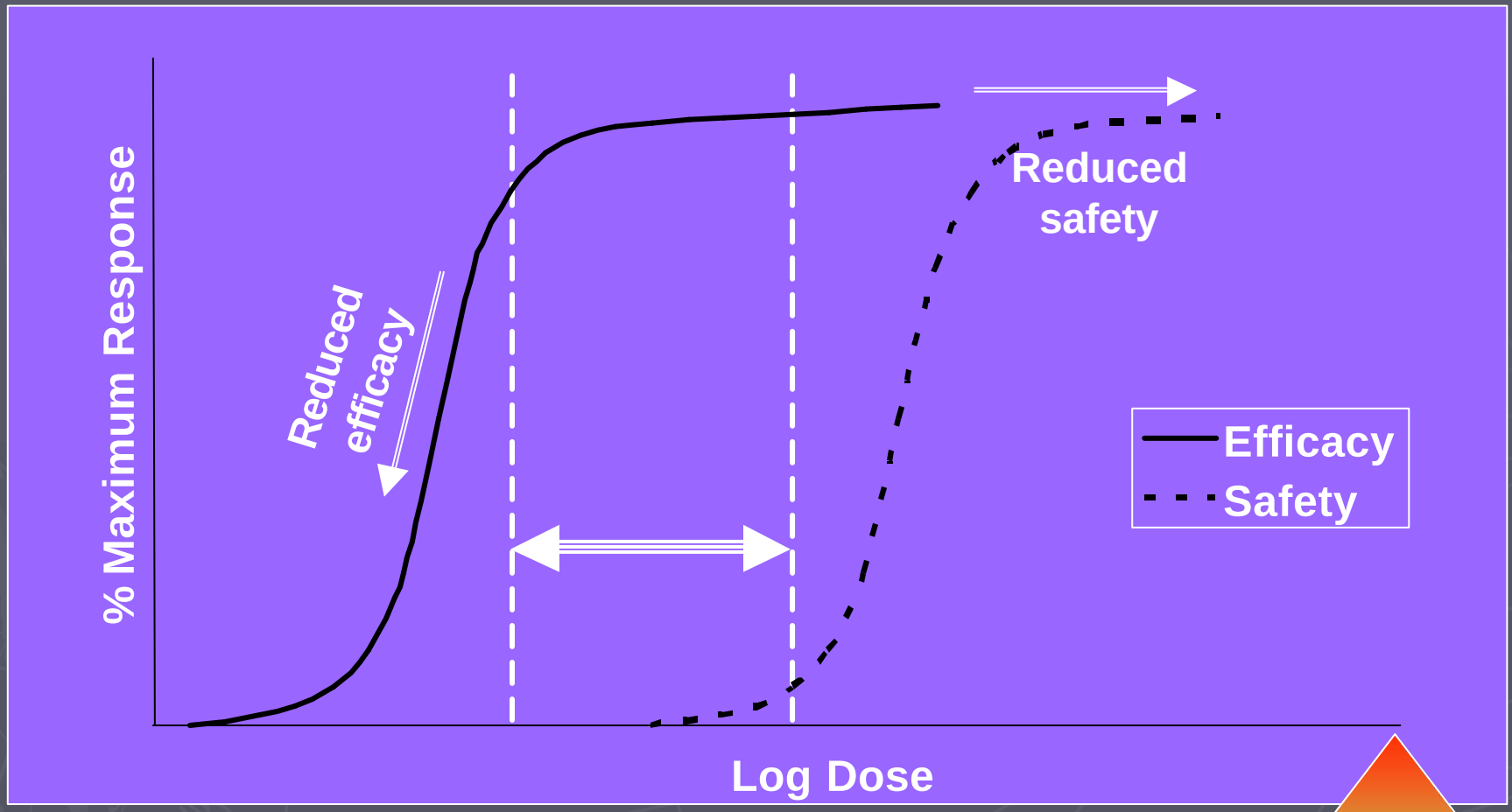
Bioequivalence

= **Therapeutic Equivalence**

(Note: Generally, same dissolution spec.)

Critical for patients and public confidence in our regulatory system

Average Dose-Response



Safety & Efficacy

Uncertainty > "The Current U.S. Procrustean Bioequivalence (BE) Guidelines"

- The manufacturer of the test product must show using two one-sided tests that a 90% confidence interval for the ratio of the mean response (usually AUC and C_{max}) of its product to that of the reference product is within the limits of 0.8 and 1.25 using log transformed data.
- **(Procrustean ° marked by an arbitrary, often ruthless disregard for individual differences or special circumstances.)**
- **Note: BCS is a non-Procrustean advance**
- **We should consider other non-Procrustean advances**

Leslie Z. Benet, Ph.D. ACPS Meeting April 14, 2004

MEMORANDUM

TO: Members, Advisory Committee for Pharmaceutical Science

FROM: Ajaz S. Hussain, Ph.D.
Chair, The Biopharmaceutic Classification System (BCS) Working Group

Date: 12 November 1997

RE: The Biopharmaceutics Classification System Guidance: Current thinking and issues for considerations

reformulated during the clinical trials and once again after the clinical trials were completed (to-be-marketed product) and bioequivalence tests were performed (clinical product A vs. clinical product B; clinical product B vs. to-be-marketed product C). Dissolution specification for these products were set at: not less than 80% released in 30 minutes in 0.1 N HCl using USP apparatus 2 at 50 rpm

BE?

Product A was prepared by a wet-granulation process and contained small particles of the drug (diameter D50% - 80 microns, D90%- 138 microns). This product disintegrated in about 10-12 minutes and dissolved about 68% in 15 minutes and 99% in 30 minutes.

Product B was prepared by direct compression and contained large particles of the drug (diameter D50%-290 microns, D90%-700 microns). This product disintegrated in about 1 minute and dissolved about 85% in 15 minutes and 95% in 30 minutes.

Advisory Committee for Pharmaceutical Science

An Update on the BCS Guidance

Waiver of In Vivo Bioequivalence Studies for Immediate Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System

Ajaz S. Hussain, Ph.D.

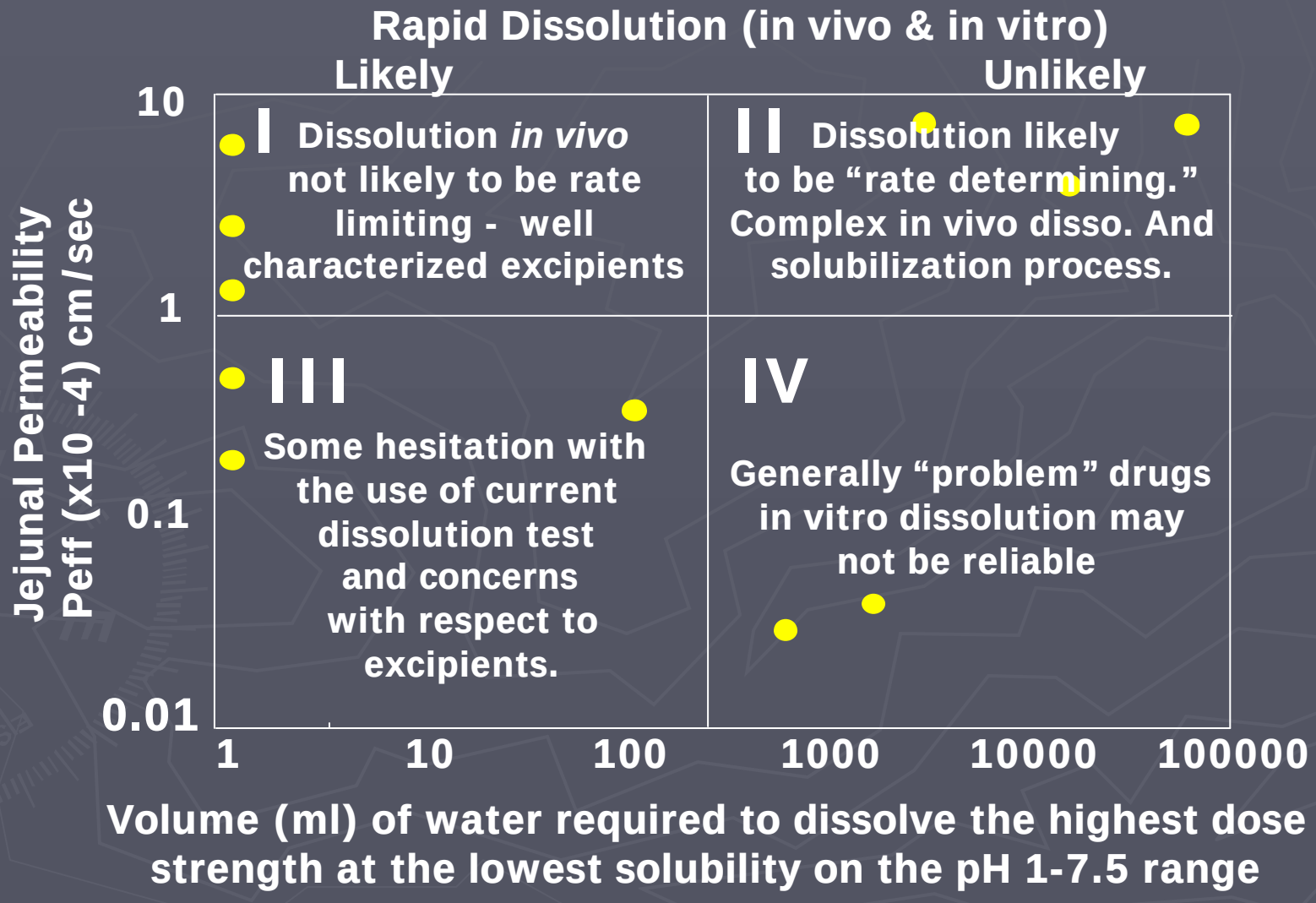
Chair, BCS Working Group

Biopharmaceutics Coordinating Committee

OPS, CDER, FDA

16 November 2000

BCS Class Membership: Risk Management



BCS a tool for risk management

- 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?

Differences in Drug Dissolution: Primary Reason for Bio-in-equivalence(?)

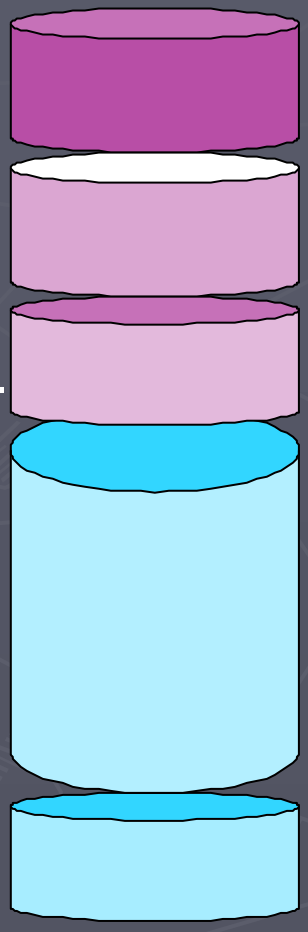
Solutions

Suspensions

Chewable, etc.

Conventional Tablets Capsules

MR Products



"Self-evident" - Biowaiver possible
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
Draft BCS
(pre-/post approval)

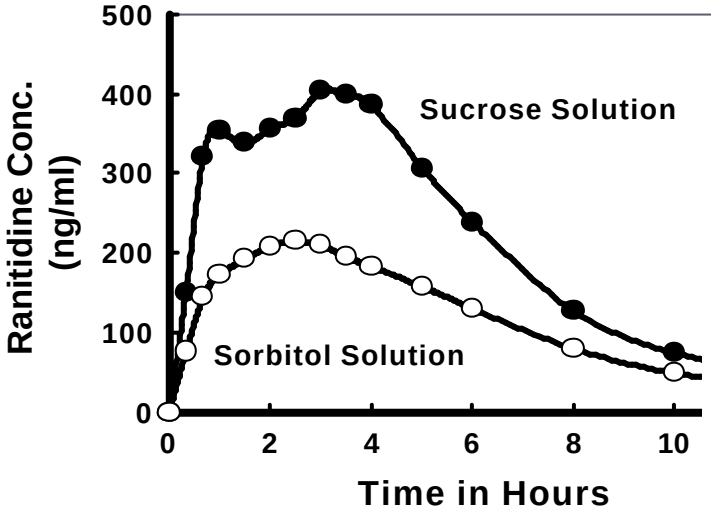
In VIVO

SUPAC-MR
IVIVC

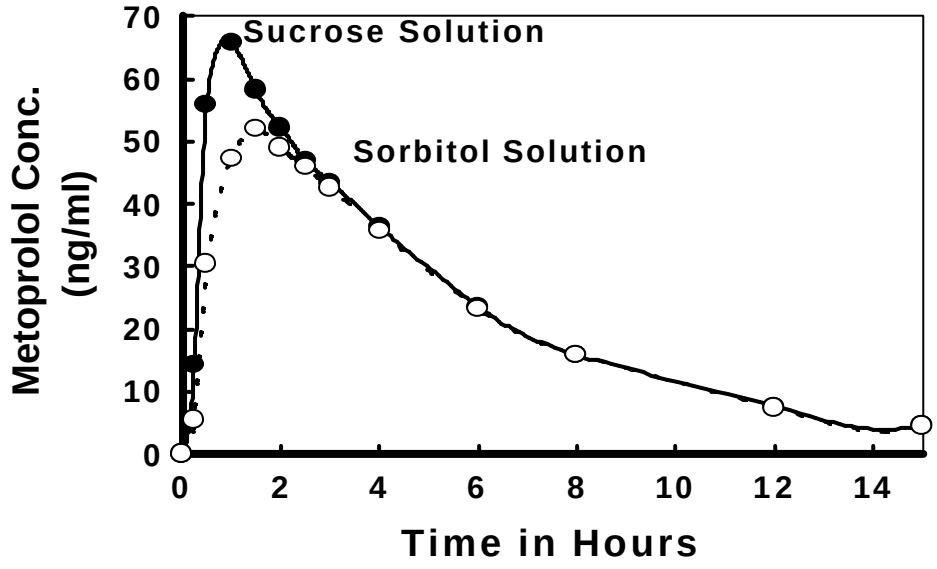
Risk Factor: Excipients

- Is the [current] approach of evaluating excipients for decisions related to biowaiver of oral solutions sufficient?
  - For BCS based biowaivers a higher standard was adopted (by limiting biowaivers to *highly permeable* drugs)
    - excipients used in solid oral products less likely to impact drug absorption compared to liquid oral product
  - *High permeability* attribute reduces the risk of bio-in-equivalence
    - decreased small intestinal residence time by osmotic ingredients
    - enhanced intestinal permeability (potentially by surfactants)

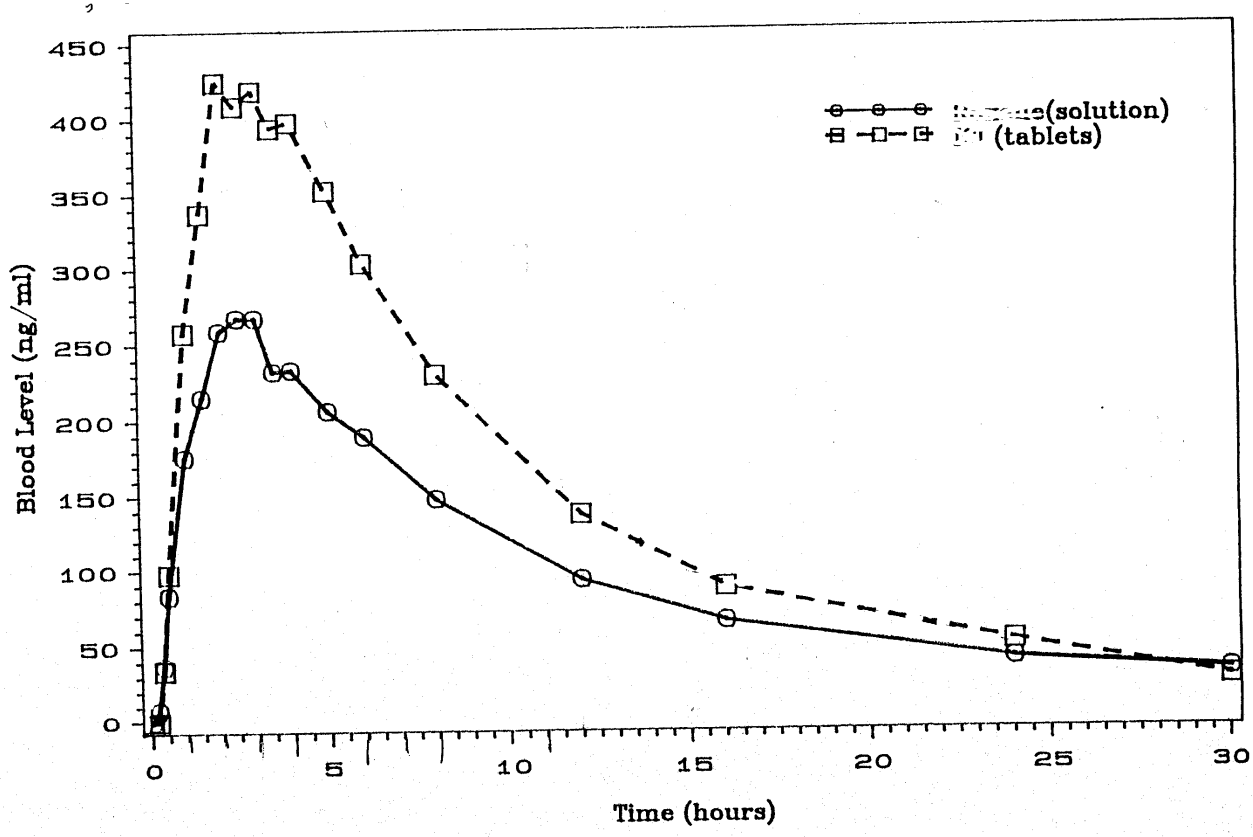
Low Permeability can pose a higher risk of bio-in-equivalence



Hussain et al, AAPS Annual Meeting 2000



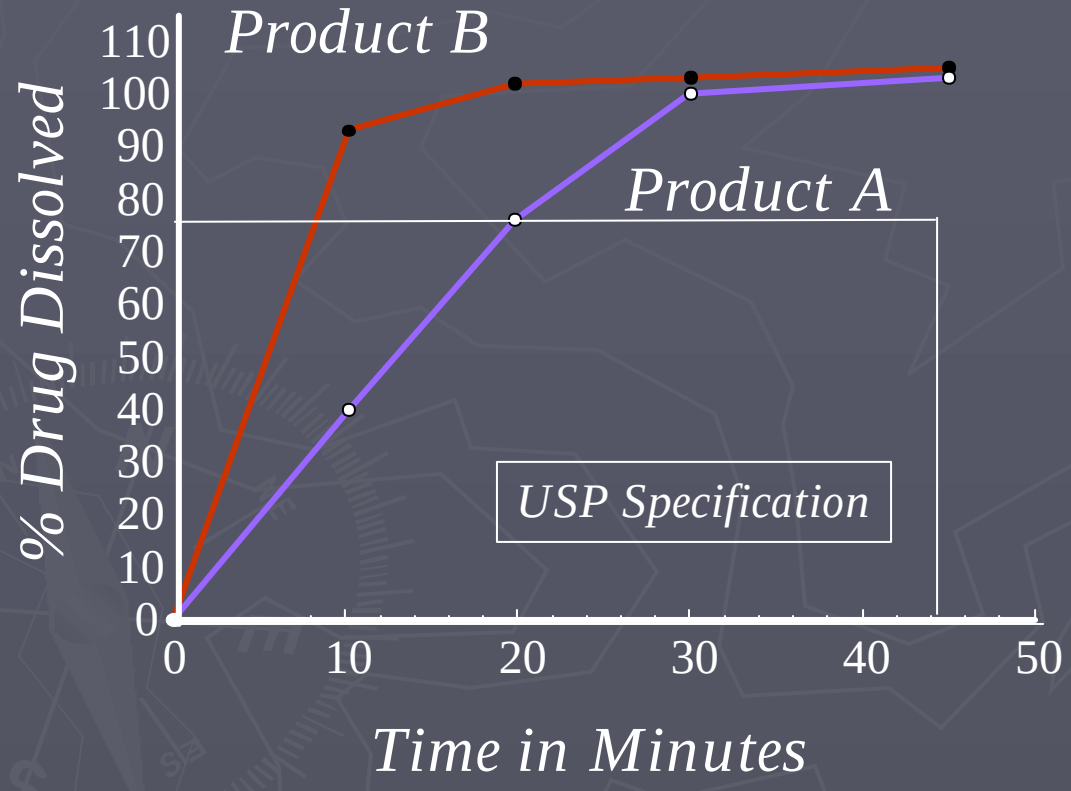
Mean Atenolol Blood Levels



Failure of Dissolution Tests to Signal Bio-in-equivalence

- Inappropriate “acceptance criteria”
  - single point criterion
- Inappropriate test method
  - media composition (pH,..)
  - media volume
  - hydrodynamics
- Excipients affect drug absorption
- Other reasons (type II error)

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

Risk Factor: Failure to emulate *in vivo* dissolution process

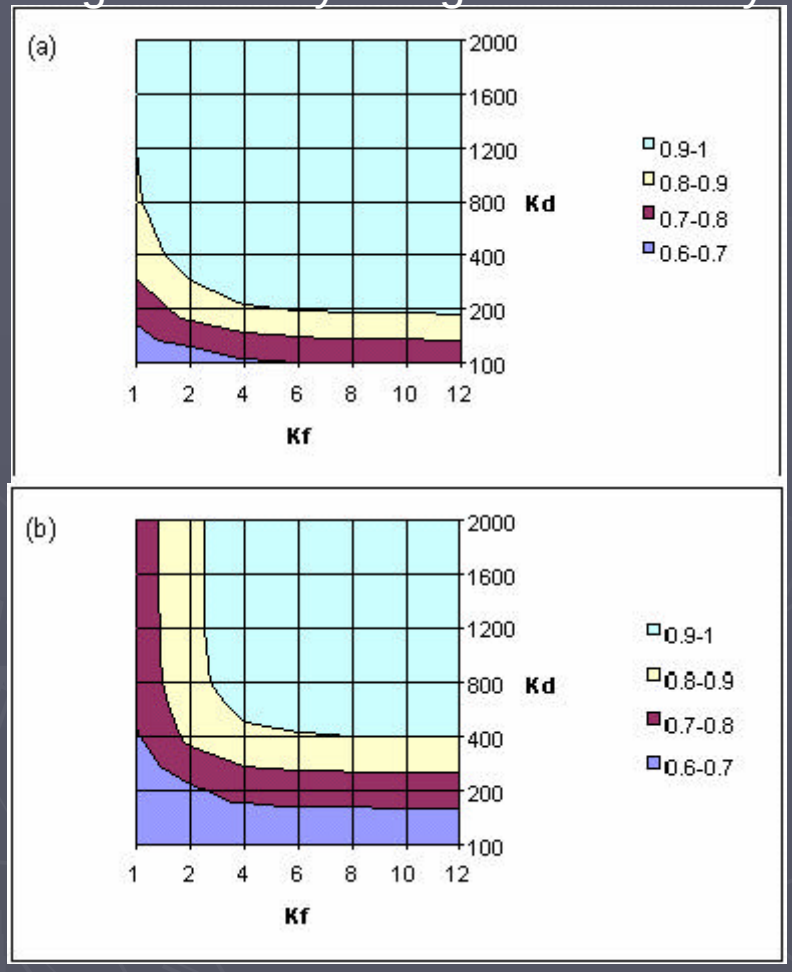
- Dissolution methods have evolved over last thirty years as test method for lot-lot quality assurance
  - Dissolution volume and composition selected to maintain “sink” conditions
    - *In vivo* solubilization (e.g., bile) is a complex process and is more critical for “low solubility” drugs
    - *In vivo* “sink” condition is due to intestinal permeability
  - Dissolution tests under certain conditions are not ‘discriminatory” (or inability to *a priori* define optimal conditions)
    - Multi-media dissolution test for biowaivers
    - Several examples for drugs with pKa in 3-6 range (rule of thumb: dissolution media pH ~ pKa of drugs (3-6))

Risk Factor: Failure to emulate *in vivo* dissolution process

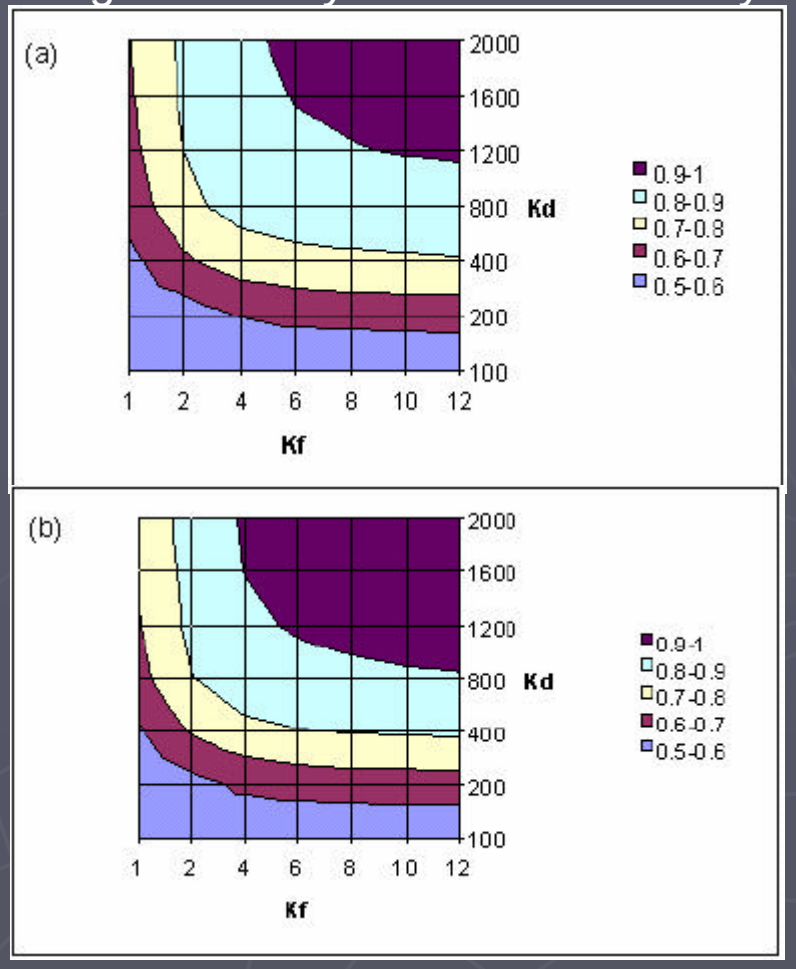
- When dissolution is slow (rate limiting) *IVIVC* have been demonstrated, however such a correlation may not hold when certain formulation changes are introduced
  - For ER products a change in release mechanism
  - For IR products of low solubility drugs (e.g., spirinolactone and carbamezapine)
  - Rapid dissolution criteria to ensure that drug dissolution is not rate limiting

- *High solubility*, *high permeability* and *rapid dissolution* are utilized to minimize the risks associated with the use of QC dissolution apparatus and conditions for decisions on biowaivers

High Solubility – High Permeability



High Solubility – Low Permeability



"...effect of disintegration of a dosage form and dissolution of drug particles depend on the permeability of a drug, with a low-permeability drug having a greater effect."

***AAPS PharmSci* 2001; 3 (3) article 24 (http://www.pharmsci.org).**

ICH Q6A DECISION TREES #7: SETTING ACCEPTANCE CRITERIA FOR DRUG PRODUCT DISSOLUTION

Building Quality In ?

What specific test conditions and acceptance criteria are appropriate? [IR]

Product Design
(Postulate - Confirmed Based on mechanism and/or empirically)

Clin. Pharm. What?

dissolution significantly affect BA?

YES

Develop test conditions and acceptance distinguish batches with **unacceptable BA**

?

NO

Design of Manufacturing and Controls
How (reliable)?

Do changes in formulation or manufacturing variables affect dissolution?

YES

Are these changes controlled by another procedure and acceptance criterion?

So what?

Overall Risk-based CMC: Why?

NO

YES

NO

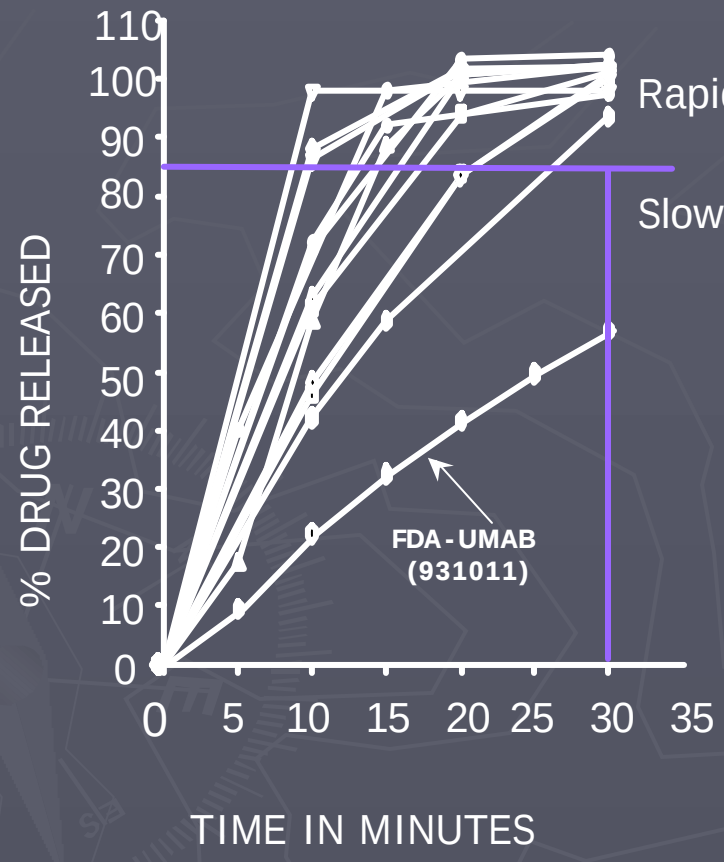
Adopt appropriate test conditions and acceptance criteria without regard to discriminating power, to pass clinically acceptable batches.

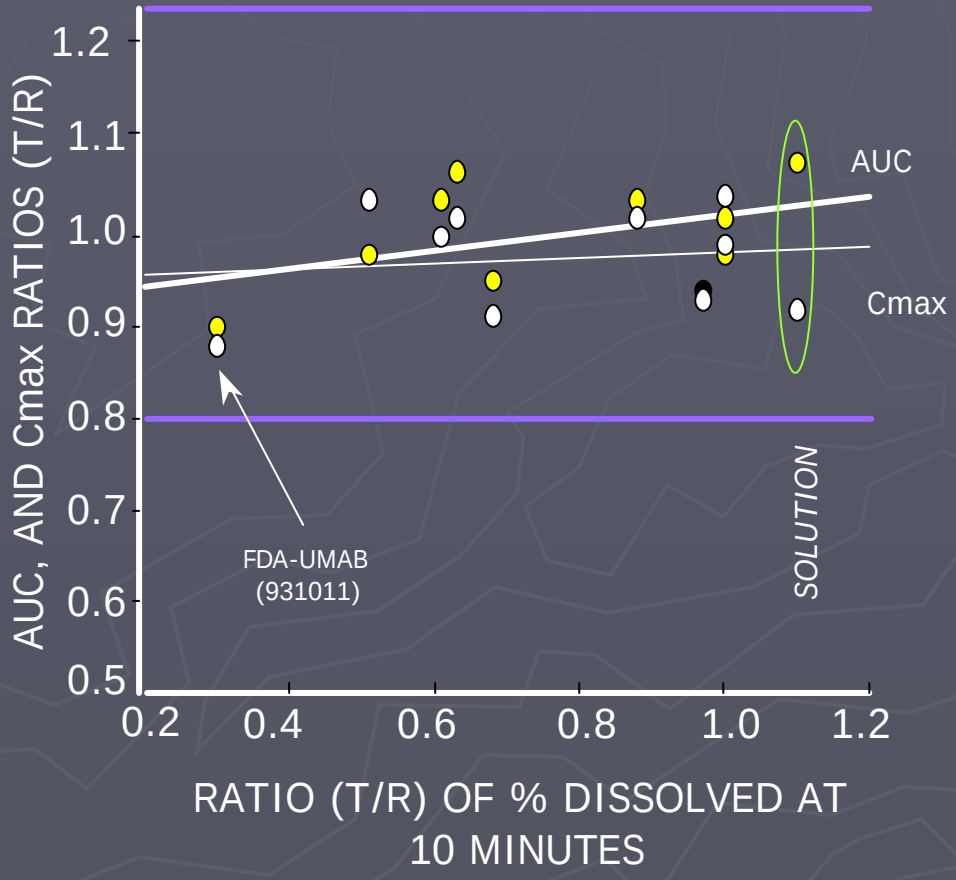
Adopt test conditions and acceptance criteria which can distinguish these changes. Generally, single point acceptance criteria are acceptable.

Appropriate Controls & Specifications

Overall CMC Systems approach (e.g., link to morphic form, particle size, stability failure mechanisms) CMC: Why? Then How?

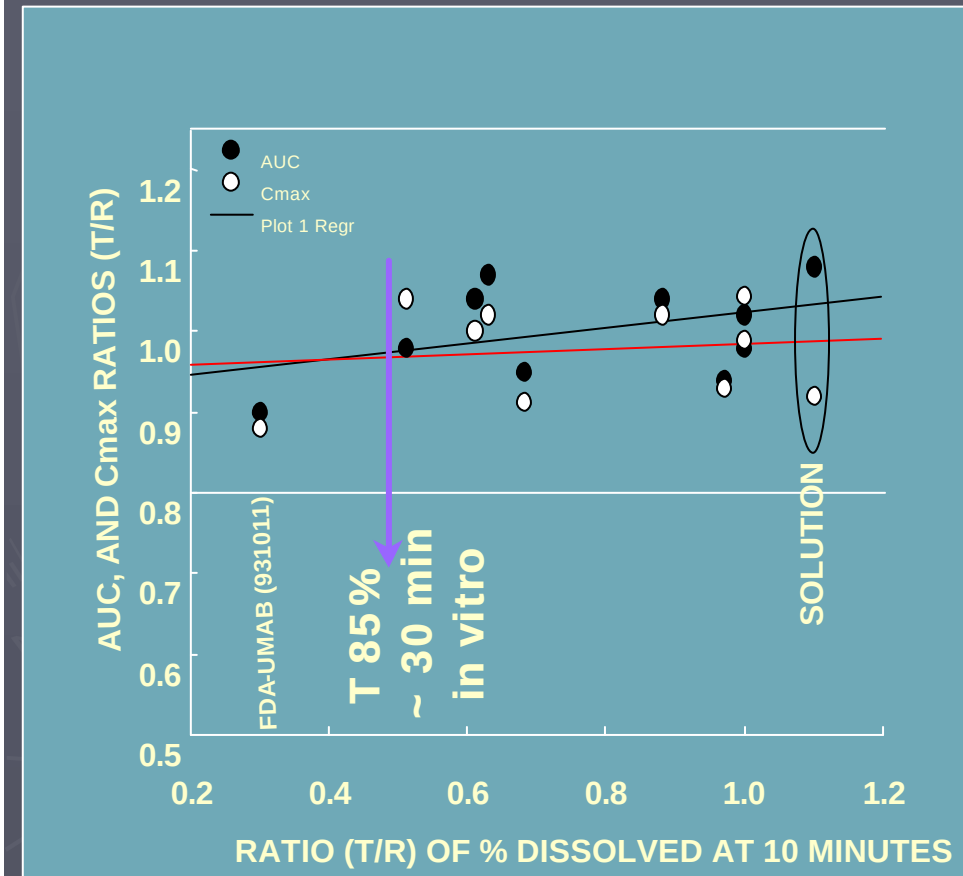
Metoprolol IR Tablets: In Vitro - In Vivo Relationship

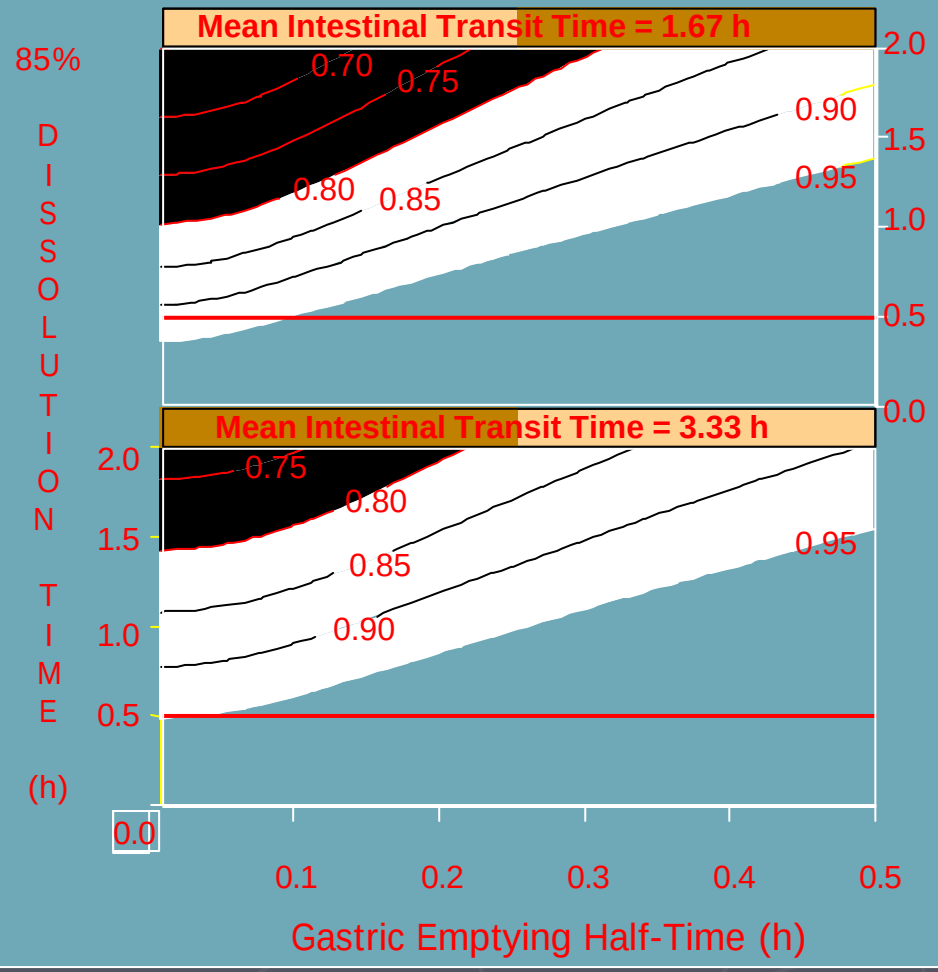




Hussain,

Metoprolol IR Tablets: Experimental & Simulation Data





Pharm Res. 1999 Feb;16(2):272-80

Dissolution - Attributes: Casual Link

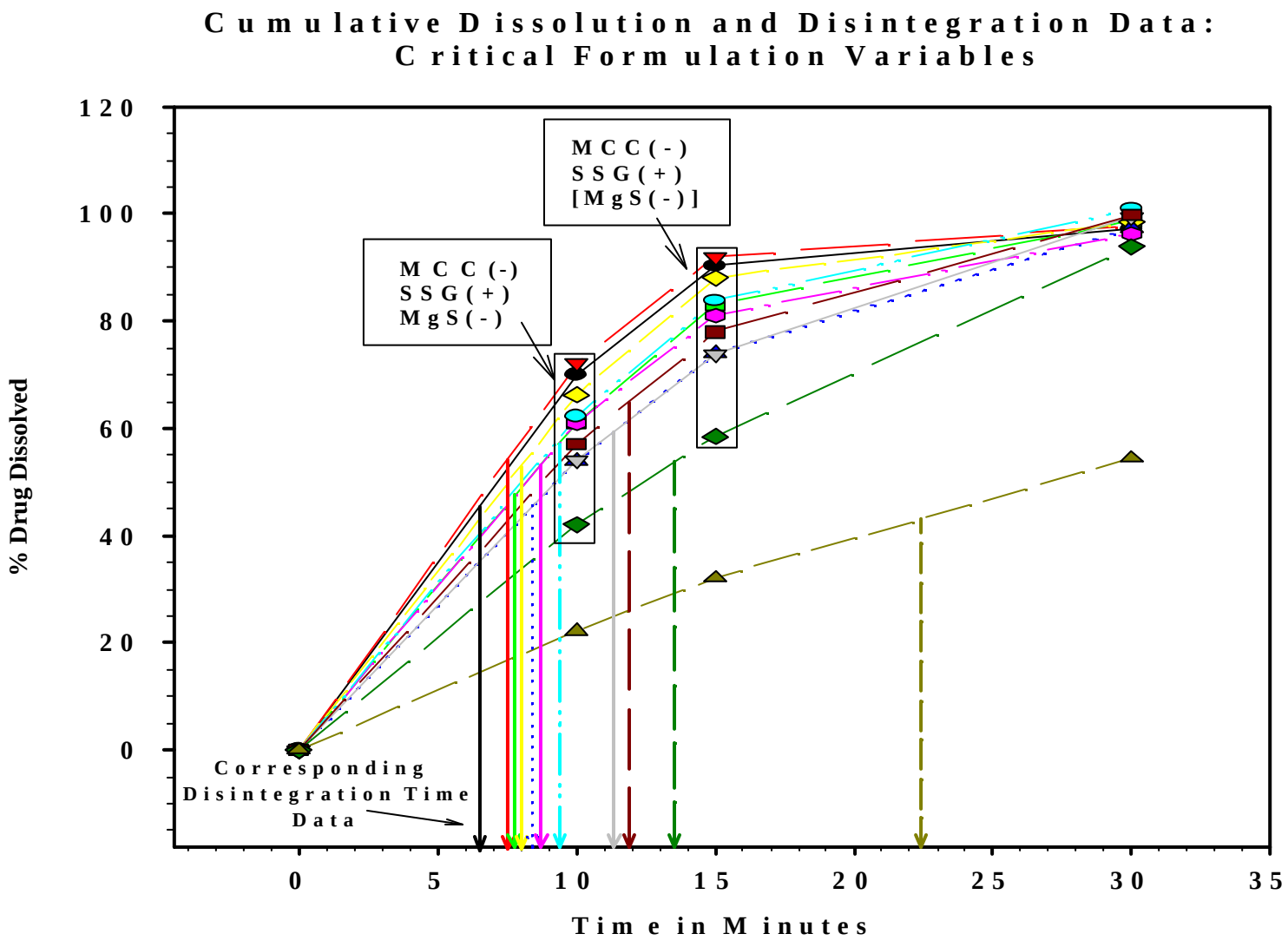
Dissolution is a function of processing variables:

$$Dissolution = f\,(Ex1, Ex2, P1, P2, PS\ldots)$$

Ex1, Ex2 = Excipients (USP/NF)
P1, P2 = Process parameters (time, hardness ...)
PS = Drug particle size (specification)

$$y = b_0 + b_1 x_1 + b_2 x_2 + b_3 x_3 + b_{12} x_1 x_2 + b_{13} x_1 x_3 + b_{23} x_2 x_3 + \ldots$$

Dissolution Test for QC/QA: What is it telling us?



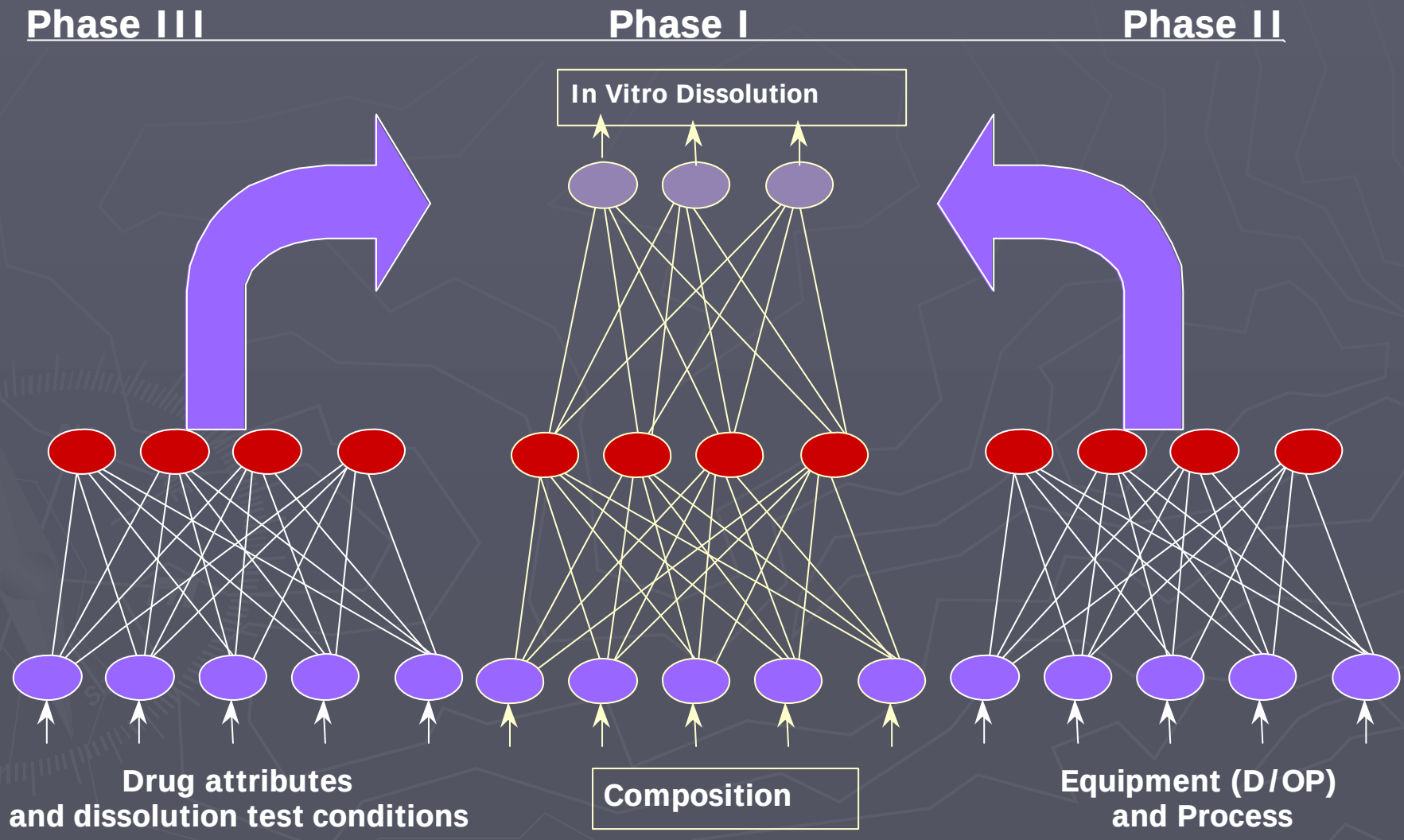
Pharm Dev Technol. 1997 Feb;2(1):11-24.

Generalization?

- Similarity between training (FDA/UMAB) and test (ANDA) formulations

FDA/UMAB	1	2	3	4	5	6	7	8	9
Binder	✔	✔	X	✔	✔	✔	✔	✔	X
Diluent A	X	X	✔	✔	X	✔	✔	✔	✔
Disint.	✔	✔	✔	✔	✔	✔	✔	✔	✔
Diluent B	✔	✔	✔	✔	✔	✔	✔	✔	X
Lubricant	✔	✔	✔	✔	✔	✔	✔	✔	✔
Granulation method	✔	✔	✔	✔	✔	✔	✔	✔	X

Prototype SUPAC-IR Network



Test Formulation	Prediction Error % : Q(10)	Prediction Error % : Q(30)
ANDA 1	-29	-15
ANDA 2	-2	-2
ANDA 3	13	13
ANDA 4	- 6	- 4
ANDA 5	25	4
ANDA 6	7	2
ANDA 7	14	-5
ANDA 8	- 4	4
ANDA 9	- 14	7
Innovator	6	-7

Formulation "Design Space" for BE?

Component	SUPAC Reco. Limit (Level 2)	Max change in component having no impact on dissolution (15% or less difference in dissolution)
Diluent A (IN)	10%	15%
Diluent A (OUT)	10%	30%
Diluent B	10%	70%
Disintegrant (IN)	2%	7%
Disintegrant (Out)	2%	3%
Binder	1%	5%
Lubricant	0.5%	2%

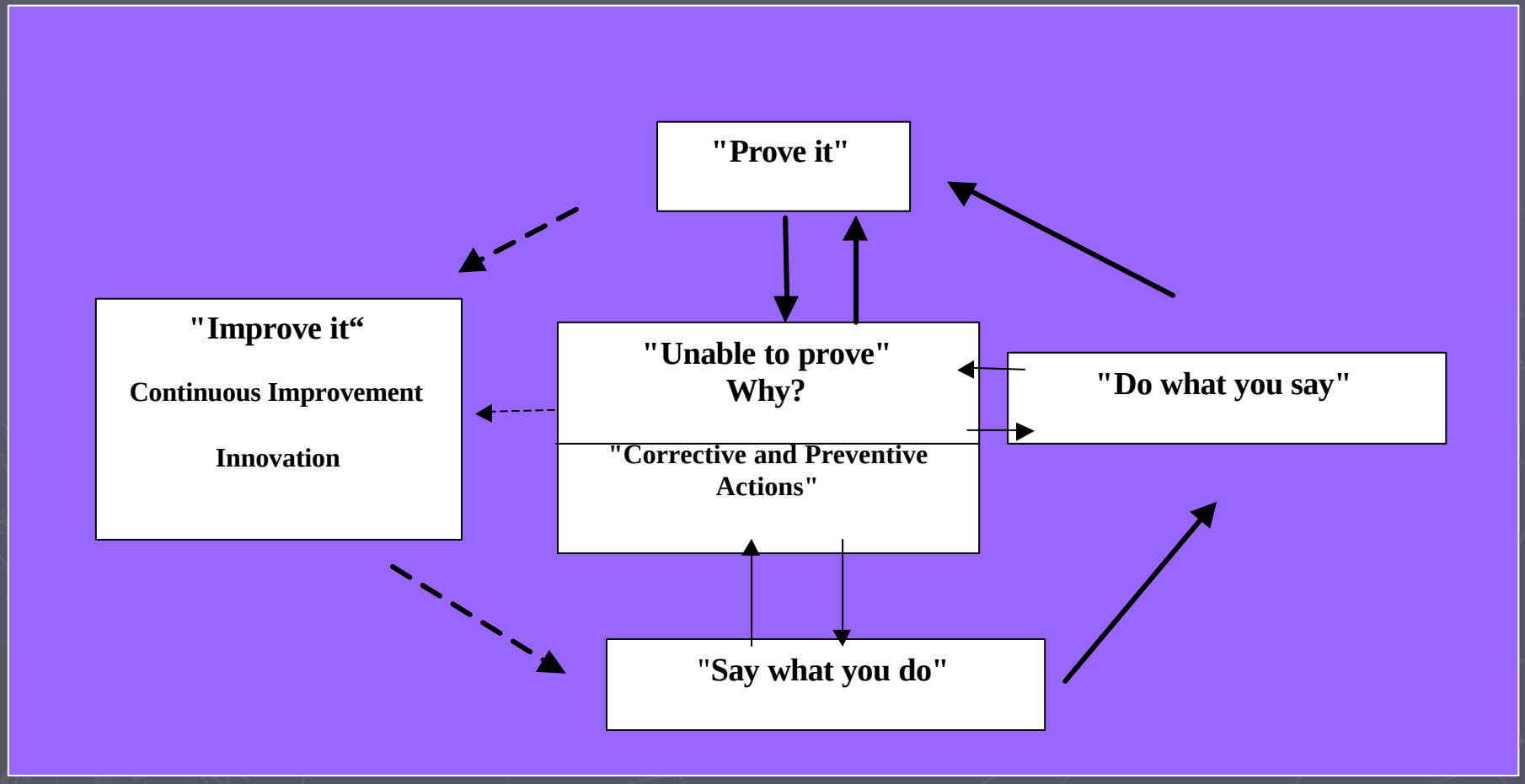
Similarly a "design space" for Shelf-Life would be needed.

Process “Design Space” for BE?

- Process options – Direct compression or wet granulation
- Equipment and process parameters based on “manufacturability” criteria
- Design space boundary – acceptable dissolution

Similarly a “design space” for Shelf-Life would be needed.

CGMP Initiative



http://www.fda.gov/cder/gmp/gmp2004/manufSciWP.pdf

The character of the questions we ask greatly influences the appropriateness of the answers we develop – ***www.systems-thinking.org***

“Learning is not compulsory…. neither is survival” W. Edwards Deming