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

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Timeline

1990	Research (FDA, MPA,Univ. Michigan, Uppsala, and Maryland)
11/1995	Application in SUPAC-IR Guidance
4/1996	BCS Working Group formed to develop a guidance
8/1996	ACPS Discussion
4/1997	AAPS/CRS/FDA Workshop
6/1997	EUFEPS 4th Int. Conference on Drug Absorption
10/1997	"Expert Panel" Meeting
12/1997	ACPS Discussion
8/1998	AAPS Workshop on Permeability Methods
10/1998	ACPS Discussion
2/1999	Draft Guidance Published
6/2000	Internal Training
8/2000	Final Guidance Published
9/2000	External Training
	Next Steps

BCS Guidance 2000

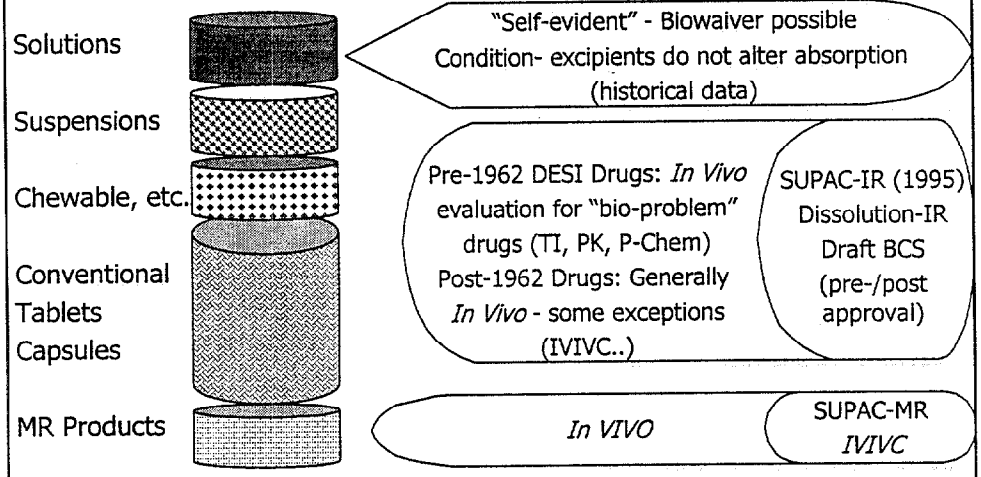
- Methods for classifying a drug based on solubility and intestinal permeability
- *Rapid dissolution* criteria
- Biowaiver for
  - *rapidly dissolving* solid oral dosage forms containing drugs that exhibit *high solubility*, *high permeability*, and *wide therapeutic index*
    - established excipients

BCS a tool for risk management

(discussion on risk management is based on R.F. Griffith. Dealing with risk. 1981)

- 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?

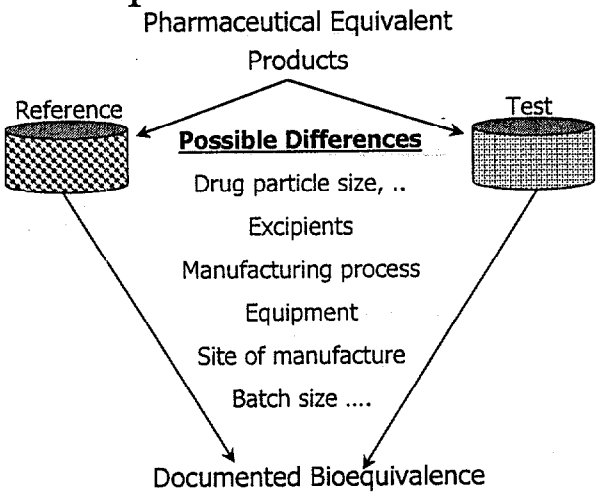
Differences in Drug Dissolution: Primary Reason for Bio-in-equivalence(?)



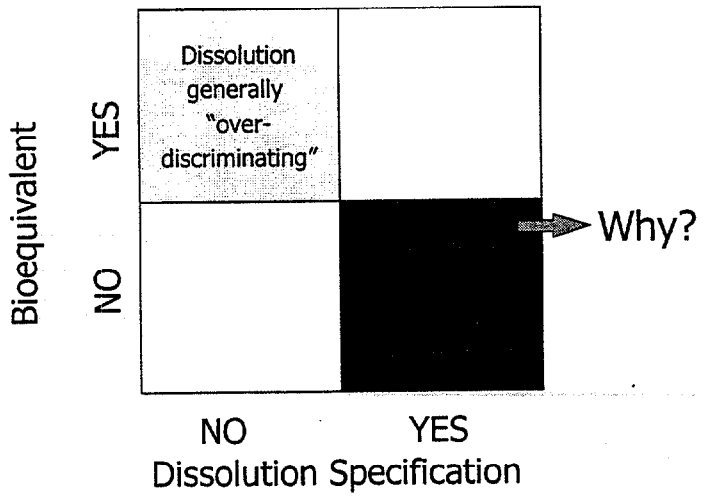
FDA's Bioequivalence Hearing (1986)

- "..seems sensible to think that swallowing something that turns into a solution rapidly would be difficult to lead to differences from one product to the next....."
  - Bob Temple in response to Arnold Becketts presentation
- "....I've learned that there is no support here for attempting to provide such assurance solely with in vitro data."
  - Milo Gibaldi

Bioequivalence: IR Products



Dissolution specifications and Bioequivalence



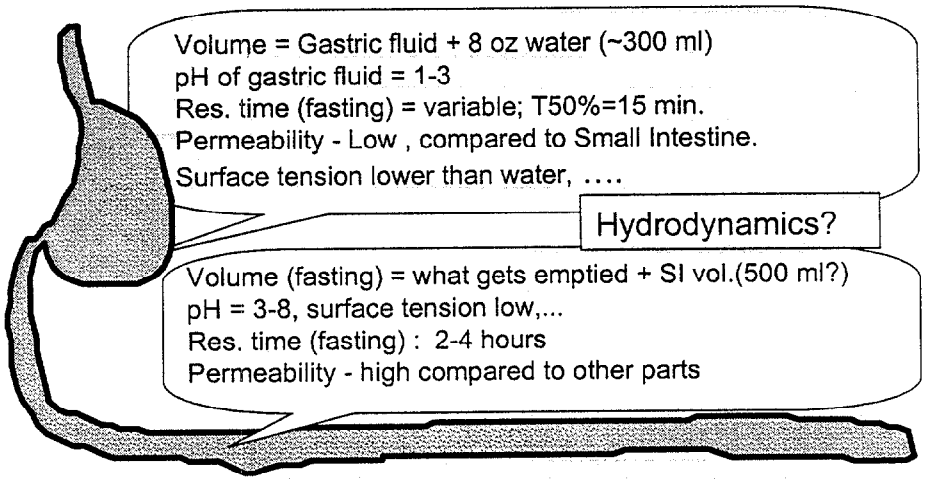
Dissolution tests: Debates

- Dissolution tests are "over discriminating"
- Products that dissolve about 70% in 45 minutes have no medically relevant bioequivalence problems
- Dissolution tests are not sufficient to assure bioequivalence
- Demonstration of IVIVC is necessary
- IVIVC's are "Product Specific"

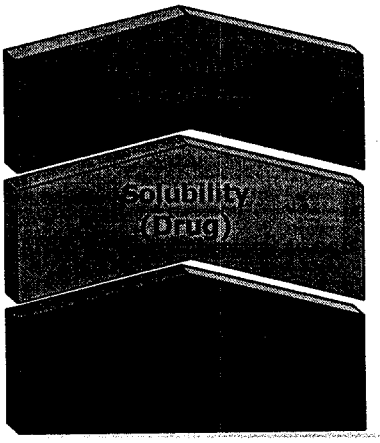
Failure of Dissolution Tests to Signal Bio-in-equivalence

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

Typical Physiologic Parameters:
Single Dose Fasting BE Study



BCS Class Boundaries: Objectives

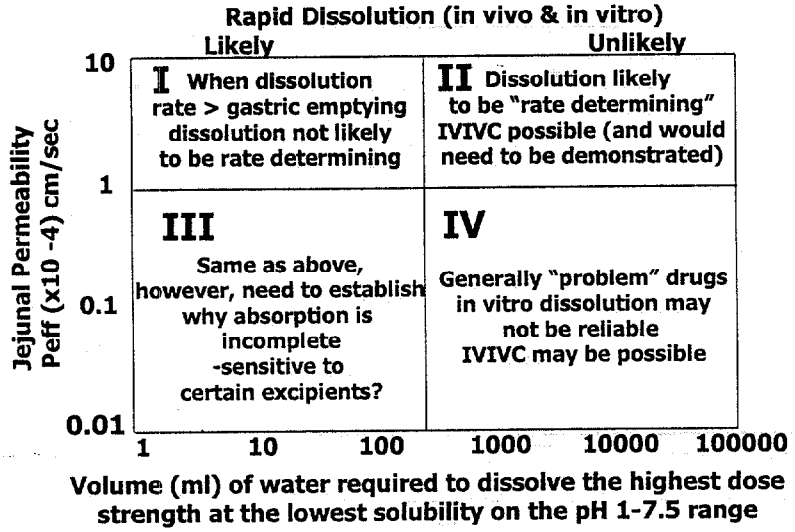


Rapid dissolution - ensure that in vivo dissolution is not likely to be the "rate determining" step

High solubility - ensure that solubility is not likely to limit dissolution and, therefore, absorption

High permeability - ensure that drug is completely absorbed during the limited transit time through the small intestine

BCS Class Membership: Risk Management



Acceptance of BCS based biowaivers

- Strong support from scientific community
  - ACPS, Experts, FDA staff, Public workshops
- Some concerns expressed at public workshops and comments on draft guidance
  - "overly conservative" - should also apply to Class III and some class II drugs
  - application for Generics
  - impact of excipients

Next Steps

- Further research
  - Extension of BCS based biowaivers
  - Application for waiver of "fed" bioequivalence studies
- Continuation of educational initiatives
  - practitioners and public
- International harmonization