What is the Role of the Pharmaceutical Scientist?

Deliver High Pharmaceutical Quality Product to the patient

What is high Pharmaceutical Quality?

- The product performs according to the label claims.
- How good are label claims?
- Pharmaceutical Standards!
- How do we set them?
Why is BE Important?

BE connects the product in the bottle with the claims on the label!
### Guidance for Industry

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

<table>
<thead>
<tr>
<th>Biopharmaceutics Class</th>
<th>Solubility</th>
<th>Permeability</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>II</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>III</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>IV</td>
<td>Low</td>
<td>Low</td>
</tr>
</tbody>
</table>

**BCS Class I Biowaivers**

**BCS Class III Biowaivers**

Recommended and Under Consideration
Systemic (BA) vs. Oral Transport View (BE)

The Science of BE is at the Absorption Site

\[ F_{\text{sys}} = F_{\text{abs}} \times F_g \times F_H \]
BCS takes a mechanistic approach to setting bioequivalence standards: Mass Transport in the GI Tract

\[ \text{Flux} = j = P_{\text{eff}} \cdot C \]
First Principle of Bioequivalence

If a drug from two products are presented to the Intestinal Surface *Equivently* they will be Bioequivalent
## Diffusion vs. Pharmacokinetic Views of Absorption

<table>
<thead>
<tr>
<th>Diffusion</th>
<th>Pharmacokinetic</th>
</tr>
</thead>
<tbody>
<tr>
<td>( J = (dM / dt)1 / A )</td>
<td>( dC / dt = (dM / dt)1 / V )</td>
</tr>
<tr>
<td>( = P \cdot \Delta C \cong P \cdot C )</td>
<td>( = k_a \cdot \Delta C \cong k_a \cdot C )</td>
</tr>
<tr>
<td>( P = \text{cm} / \text{sec}. )</td>
<td>( k_a = 1 / \text{sec} )</td>
</tr>
</tbody>
</table>

\[ k_a = (S / V) \cdot P_{\text{eff}} \]

Software e.g. GastroPlus®
Absorption Rate Coefficient: \( k_a \sim \text{Local Permeability}(P_{eff}) \)

Transport

\[
J = (1 / A)(dM / dt) = P_{eff} \cdot C
\]

PK

\[
dC / dt = (1 / V)dM / dt = k_a C
\]

Permeability \sim Absorption Rate Coefficient(constant)

Equating \( dM / dt \):

\[
A \cdot P_{eff} \cdot C = V \cdot k_a C
\]

\[
k_a = (A / V)P_{eff}
\]

\[
k_a = (2 / R)P_{eff} \approx P_{eff}
\]

\[
R \sim 2cm(1.75)
\]

\[
k_a \sim P_{eff}
\]

Numerically (Units differ: 1/sec vs. cm/sec)
BCS takes a mechanistic approach to setting bioequivalence standards: Mass Transport in the GI Tract

\[
\text{Flux} = j = P_{\text{eff}} \cdot C
\]
Biopharmaceutics Classification System (BCS): Basis

\[ M(t) = \int_0^t \int_A (P_{\text{eff}} \cdot C) dA dt \]

Absorption per unit area per unit time
Why is BE Important?

BE connects the product in the bottle with the claims on the label!
Bioequivalence (BE) Today

- Historically a Relative Bioavailability (BA) Based View
  - Misses the underlying scientific issues
    - IN Vivo Dissolution

- BE Testing is Same Drug
  - Once Absorbed PK is the Same

- The Science of BE is at the Absorption Site
  - For Oral Dosage Form in the GI Tract

- The Question is: What is the Best BE Test
Systemic (BA) vs. Gut View (BE)

The Science of BE is at the Absorption Site
Ejemplo de test de Bioequivalencia a partir del Cmáx:

Perfiles de concentración del fármaco problema:

¿Bioequivalente? ¿Bioequivalente? ¿Bioequivalente?
BCS takes a mechanistic approach to setting bioequivalence standards: Mass Transport in the GI Tract

\[ Flux = j = P_{\text{eff}} \cdot C \]
Guidance for Industry

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

Guidance for Industry

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

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
August 2000

| Note | This revised Note for Guidance will replace the previous guideline adopted in December 1991. |

COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS (CPMP)

NOTE FOR GUIDANCE ON THE INVESTIGATION OF BIOAVAILABILITY AND BIOEQUIVALENCE

| DISCUSSION IN THE JOINT EFFICACY AND QUALITY WORKING GROUP | December 1998 – October 1999 |
| TRANSMISSION TO CPMP | July 1999 |
| RELEASE FOR CONSULTATION | December 1998 |
| DEADLINE FOR COMMENTS | June 1999 |
| DISCUSSION IN THE DRAFTING GROUP | February – May 2000 |
| TRANSMISSION TO CPMP | July – December 2000 |
| RELEASE FOR CONSULTATION | December 2000 |
| DEADLINE FOR COMMENTS | March 2001 |
| DISCUSSION IN THE DRAFTING GROUP | March – May 2001 |
| TRANSMISSION TO CPMP | July 2001 |
| ADOPTION BY CPMP | July 2001 |
| DATE FOR COMING INTO OPERATION | January 2002 |
FDA/BCS, EMA/CPMP, WHO BE Recommendations (2000-2010)

Guidance for Industry

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

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
August 2000

Guidance on Availability and Bioequivalence

<table>
<thead>
<tr>
<th>GUIDANCE ON AVAILABILITY AND BIOEQUIVALENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>CY AND QUALITY</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
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<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

Committee for Medicinal Products for Human Use (CHMP)

WHO Expert Committee on Specifications for Pharmaceutical Preparations

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

DRAFT

GUIDELINE ON THE INVESTIGATION OF BIOEQUIVALENCE

DRAFT AGREED BY THE EFFICACY WORKING PARTY

ADOPITION BY CHMP FOR RELEASE FOR CONSULTATION

END OF CONSULTATION (DEADLINE FOR COMMENTS)

The guideline will replace the "Note for guidance on the investigation of bioavailability and bioequivalence" CPMP/ICH/396/98 and the related questions in the CHMP document CPMP/ICH/2104/98. This guideline includes recommendations on BCS-based bioequivalence.

Comments should be provided to CHMP@ema.europa.eu using this template.

KEYWORDS: dissolution, pharmacokinetics, formulation, in vivo absorption, genotoxic.
WHO Expert Committee on Specifications for Pharmaceutical Preparations

Fortieth Report

World Health Organization

Geneva

WHO Technical Report Series

Annex 7
page 347

Annex 8
page 391

Table 1

<table>
<thead>
<tr>
<th>Medicine*</th>
<th>Highest oral strength according to WHO Essential Medicines List*</th>
<th>Solubility*</th>
<th>Permeability*</th>
<th>ICS class*</th>
<th>Classification test (for bioavailability)**</th>
<th>Indication(s) according to WHO Essential Medicines List*</th>
<th>Comments and special dosage form indication*</th>
</tr>
</thead>
<tbody>
<tr>
<td>atenolol</td>
<td>200 mg</td>
<td>high</td>
<td>low</td>
<td>3</td>
<td></td>
<td>9.2.1.2</td>
<td>antimicrobial</td>
</tr>
<tr>
<td>acetaminophen</td>
<td>250 mg</td>
<td>low</td>
<td>low (7)</td>
<td>4.2</td>
<td>Not eligible for bioavailability</td>
<td>9.2.1.1</td>
<td>unknown whether poor BA is due to poor solubility and/or poor permeability</td>
</tr>
<tr>
<td>acetaminophen</td>
<td>500 mg</td>
<td>high</td>
<td>high</td>
<td>1</td>
<td></td>
<td>9.2.1.1</td>
<td>nonsteroidal anti-inflammatory medicine</td>
</tr>
<tr>
<td>acetaminophen</td>
<td>100 mg</td>
<td>high</td>
<td>high</td>
<td>1</td>
<td></td>
<td>9.2.1.1</td>
<td>analgesic</td>
</tr>
<tr>
<td>acetaminophen</td>
<td>200 mg</td>
<td>high</td>
<td>high</td>
<td>3</td>
<td></td>
<td>9.2.1.2</td>
<td>anti-inflammatory</td>
</tr>
<tr>
<td>ibuprofen</td>
<td>400 mg</td>
<td>low</td>
<td>low (7)</td>
<td>4.2</td>
<td>Not eligible for bioavailability</td>
<td>9.2.1.1</td>
<td>sustained-release tablet; unknown whether poor BA is due to poor solubility and/or poor permeability</td>
</tr>
<tr>
<td>ibuprofen</td>
<td>100 mg</td>
<td>high</td>
<td>high</td>
<td>1</td>
<td></td>
<td>9.2.1.1</td>
<td>anti-inflammatory</td>
</tr>
<tr>
<td>ibuprofen hydrochloride</td>
<td>500 mg</td>
<td>high</td>
<td>high</td>
<td>1</td>
<td></td>
<td>9.2.1.1</td>
<td>pain</td>
</tr>
</tbody>
</table>

*NOTE: Non-essential anti-inflammatory drug, BA: bioavailability

**I,M: Immediate release, M: Modified release
FRAMEWORK FOR IMPLEMENTATION OF EQUVALENCE REQUIREMENTS FOR PHARMACEUTICAL PRODUCTS
Document for Public Opinion
WORKING GROUP ON BE
WHO (BE) Recommendations

- Solubility and Permeability
  - Same as (~)FDA and EMEA
    - Dissolution and solubility pH=6.8 (rather than 7.5)
- Dissolution: Very Rapid, Rapid, Not Rapid
- Recommends Classes for drugs on (WHO) EML
- Recommends dissolution ‘Biowaivers’ for Class I, III, and some Class II Drugs (IIa)
- Extends BCS Biowaivers to 60% of Drug Products
What is the BCS? Permeability and Solubility Classification

The BCS is a scientific framework for classifying drugs based on their aqueous solubility and intestinal permeability and setting the best Bioequivalence Test.

<table>
<thead>
<tr>
<th>Biopharmaceutics Class</th>
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<tr>
<td>III</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>IV</td>
<td>Low</td>
<td>Low</td>
</tr>
</tbody>
</table>
Biopharmaceutics Classification System (BCS): Basis

\[ M(t) = \int_{0}^{t} \int_{A} (P_{\text{eff}} \cdot C) \, dA \, dt \]

Absorption per unit area per unit time
Maximum Flux (Absorption)

\[\frac{dM}{dt} \left( \frac{1}{A} \right) = J_{\text{max}} = P_{\text{eff}} \cdot C_s\]

= Mass Absorbed per Unit Time per Unit Area

\[C_s = \text{Solubility}\]
High Solubility Drug

- $V_s = \text{Volume of Solution} < 250 \text{ ml}$
- pH = 1 - 7.5
- Highest Dose Strength
- $D_o = \text{Dose} / 250 / C_s < 1$

FDA Glass of Water = 8 oz. (240 ml)
Diffusion vs. Pharmacokinetic Views of Absorption

**Diffusion**

\[ J = \frac{(dM / dt)A}{P} \]

\[ = P \cdot \Delta C \approx P \cdot C \]

\[ P = \text{cm/ sec.} \]

**Pharmacokinetic**

\[ \frac{dC}{dt} = \frac{(dM / dt)A}{V} \]

\[ = k_a \cdot \Delta C \approx k_a \cdot C \]

\[ k_a = \frac{1}{\text{sec}} \]

\[ k_a = \left( \frac{S}{V} \right) \cdot P_{eff} \]

Software e.g. GastroPlus®
Human Permeability


Intestinal segment will be rinsed with 37°C normal saline at a flow rate of 3 m/min for at least 20 minutes until a clear and bile-free effluent is collected.

Drainage of bile
Human Jejunal Permeability (The ‘Gold’ Standard)

Intestinal permeability and its relevance for absorption and elimination

H. LENNERSNAS

Digestive Systems, Uganda University, Uganda, Kampala

(Rceived 21 September 2006 accepted 22 September 2007)

Abstract

Human intestinal permeability (IP) is determined in the intestinal region with the highest expression of enterocytes present and depends on surface area. Intestinal IP is often based on multiple parallel transport processes. The basal intestinal permeability reflects the permeability of intact intestinal mucosa. This is vital for approximating the intrinsic and dose absorption of oral drug delivery with a target IP. In contrast, the IP of the ileum will be completely absorbed at least 80% of the dose because of the ileal corkscrew. Many drugs that are significantly absorbed in vivo have a rapid and complete intestinal absorption, which is directly related to the IP values. The ileal IP for drugs transported by absorptive carriers (e.g., prodrugs and amino acid transporters) will accurately predict the kinetics of drug absorption. The data also show that even the human intestinal epithelium has a large area towards large and hydrophilic compounds, and the peptide carrier has a low contribution for compounds smaller than approximately molecular weight 1000. There is a need for more precise in vitro studies to study drug absorption and tissue distribution in the intestine. This investigation has developed a new primary model to study intestinal permeability and its function for an accurate physiologically based pharmacokinetic modeling of oral drug absorption.

Keywords: Intestinal permeability, ileal absorption, ileal efflux, drug absorption, hydrophilic, lipophilic, multidrug transporter, sodium, glucose, amino acid, folate, flavonoids

Introduction

The gastrointestinal tract is the major absorption site for many nutrients and drugs. It mediates both nutrient delivery and at the same time acts as an efficient barrier against potentially hazardous substances and toxins. Further, gastrointestinal

Table 1. Intestinal permeability (IP) characterization of 26 drugs based on their effective permeability (EP) and time release. Each figure was determined at three to five permeation experiments in human with a single approach at pH 7.4 (phosphate buffer) and various ionized conditions. Twenty-four of the drugs was evaluated in Uganda University, Kampala, and five was evaluated at the University of Helsinki, Uusikaupunki.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Human</th>
<th>Dose saturation*</th>
<th>IP-Glass</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ileum</td>
<td>5.20</td>
<td>0.50</td>
<td>100</td>
<td>50</td>
</tr>
<tr>
<td>Aminophylline</td>
<td>1.50</td>
<td>0.15</td>
<td>1</td>
<td>95</td>
</tr>
<tr>
<td>Atropalectin</td>
<td>3.00</td>
<td>0.30</td>
<td>100</td>
<td>75</td>
</tr>
<tr>
<td>Carprofen</td>
<td>3.80</td>
<td>0.20</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>0.50</td>
<td>0.00</td>
<td>100</td>
<td>50</td>
</tr>
<tr>
<td>Gammapyrine</td>
<td>0.50</td>
<td>0.05</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Indomethacin</td>
<td>1.00</td>
<td>0.10</td>
<td>100</td>
<td>95</td>
</tr>
<tr>
<td>Ketoprofene</td>
<td>1.50</td>
<td>0.50</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Lactose</td>
<td>3.00</td>
<td>0.00</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Mesalamine</td>
<td>2.50</td>
<td>0.05</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Metaxacine</td>
<td>3.50</td>
<td>0.00</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Piroxicam</td>
<td>1.50</td>
<td>0.00</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Prednisolone</td>
<td>0.50</td>
<td>0.00</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Propranolol</td>
<td>1.00</td>
<td>0.00</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Salmefetamine</td>
<td>1.00</td>
<td>0.00</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>1.50</td>
<td>0.50</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Tryptophane</td>
<td>0.50</td>
<td>0.00</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

*IP was determined at a concentration based on the most relevant, current dose determined in vivo. For low dose concentrations, the highest permeability concentrations were applied.

**High permeability due to multidrug transporter, not included in IP calculations.

Figure 2. Human jejunal permeability values ($P_{eff}$) were determined by the use of a single-pass perfusion technique (Loo-I-Gut) in human jejunum. These human $P_{eff}$ have been correlated to the fraction dose absorbed ($F_a$) of oral doses for a large number of drugs from different pharmacological classes which consequently represent structural diversity. Human jejunal permeability values for 42 compounds (31 drugs) were determined over a period of 18 years by applying this clinical technique and are presented in Tables I and II (Lennernäs et al. 1992, 1993, 1994, 1997a, 2002b; Fagerholm et al. 1995, 1996, 1997, 1999; Lindahl et al. 1996; Lennernäs 1997, 1998; Soderholm et al. 1997; Takamatsu et al. 1997, 2001; Sandstrom et al. 1998b, 1999b; Winiewicz et al. 1998, 2003; Sun et al. 2002; Chin et al. 2003; Perri et al. 2003, 2006b; Tannergren et al. 2003a, b, 2004).
Human Fraction Absorbed vs. Jejunal Permeability pH=6.5

Sun et.al *Pharm. Res.* 19, 1400, 2002
Human Permeability

Tissue Culture Permeability

**SUBJECT**
- Caco-2 cell line
- Cell preparation

**EQUIPMENT**
- Materials

**EXPERIMENT**
- Uptake Study
- Transport Study
- Data Analysis
Human Caco-2 Permeability Correlation

\[
\log Y = 0.6532 \log X - 0.3036, \quad R^2 = 0.7276 \quad \text{(all drugs)}
\]

\[
\log Y = 0.7524 \log X - 0.5441, \quad R^2 = 0.8492 \quad \text{(passive diffusive drugs)}
\]
In Silico
(Computational)

- US: 113 oral IR drugs (56.5%)
- GB: 102 oral drugs (51.0%)
- ES: 106 oral drugs (53.0%)
- JP: 113 oral drugs (56.5%)
- KR: 87 oral drugs (43.5%)

Based on 200 top-selling drug products in 5 countries, and WHO Essential drugs, drug databases of Combined List (346 drugs), Western List (147 drugs), Eastern List (163 drugs) was made and analyzed on molecular properties and BCS classification.
Comparison of the provisional BCS classification of *in silico* vs. referenced solubility approaches on 185 oral IR drugs
BCS and Dissolution: The Future

- Oral BE is a scientific question of *in vivo* Dissolution
- The *in vivo* Dissolution System (Gastrointestinal Tract) is complex
- We need to establish *in vitro* Dissolution Systems
- Need to Develop: Bioperformance Dissolution Methods (BDM)
### BE Dissolution Proposal (Starting Point)

<table>
<thead>
<tr>
<th>BCS Class</th>
<th>Drug Solubility pH 1.2</th>
<th>Drug Solubility pH 6.8</th>
<th>Drug Permeability</th>
<th>Preferred Procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>High</td>
<td>High</td>
<td>High</td>
<td>&gt;85% Dissolution in 15 min; 30 min, f2., pH = 6.8.</td>
</tr>
<tr>
<td>II-A</td>
<td>Low</td>
<td>High</td>
<td>High</td>
<td>15 min at pH=1.2, then 85% Dissolution in 30 min., pH = 6.8; F2&gt;50; 5 points minimum; not more than one point &gt; 85%.</td>
</tr>
<tr>
<td>II-B</td>
<td>High</td>
<td>Low</td>
<td>High</td>
<td>&gt;85% Dissolution in 15 min., pH = 1.2.</td>
</tr>
<tr>
<td>II-C</td>
<td>Low</td>
<td>Low</td>
<td>High</td>
<td>15 min at pH=1.2; then 85% Dissolution in 30 min., pH = 6.8 plus surfactant*; F2&gt;50; 5 points minimum, not more than one point &gt; 85%.</td>
</tr>
<tr>
<td>III</td>
<td>High</td>
<td>High</td>
<td>Low</td>
<td>&gt;85% Dissolution in 15 min., pH = 1.2, 4.5, 6.8.</td>
</tr>
<tr>
<td>IV-A</td>
<td>Low</td>
<td>High</td>
<td>Low</td>
<td>15 min. at pH = 1.2; then 85% Dissolution in 30 min., pH = 6.8.; F2&gt;50; 5 points minimum.; not more than one point &gt; 85%.</td>
</tr>
<tr>
<td>IV-B</td>
<td>High</td>
<td>Low</td>
<td>Low</td>
<td>&gt;85% Dissolution in 15 min., pH = 1.2.</td>
</tr>
<tr>
<td>IV-C</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>15 min at pH=1.2; then 85% Dissolution in 30 min., pH = 6.8 plus surfactant*; F2&gt;50; 5 points minimum, not more than one point &gt; 85%.</td>
</tr>
</tbody>
</table>
BCS Dissolution Proposal

- This is too much to digest in one seminar
- The USP cannot do this because of its charter
- The FDA cannot do this because of the legal basis for proprietary information
- This is how we do business (develop products)
BCS and Dissolution

Conclusions

- New BE Paradigm
- Reduce Unnecessary *In Vivo* Studies
- Increase Oral Product Quality
- Based on Scientific Principles and Extendable
  - E.g. Food Effects
- It is up to us!

Movement of Drug Through GI Tract: