Permeability Classification of Highly Variable Drugs

Vatsala Naageshwaran
Associate Director, Scientific Operations
**Oral Drug Absorption**

**Bioequivalence (BE):** Absence of a significant difference in the rate and extent of drug absorption between test and RLD.

- **Fa** is the fraction of the drug that is absorbed from the intestinal lumen to the intestinal enterocytes.
- **Fg** is the fraction of the unmetabolized drug in the enterocytes. **Fa × Fg** reaches the portal vein.
- **Fh** is the fraction of the unmetabolized drug in the liver. **Fa × Fg × Fh** reaches systemic circulation.

**Bioavailability (F%)** = “the rate and extent to which an active moiety becomes available in the systemic circulation.”
Absorptive Flux

\[ J = C_{\text{int}} \cdot P_{\text{wall}} \]

- \( J \): Absorptive Flux (J)
- \( C_{\text{int}} \): Concentration in lumen
- \( P_{\text{wall}} \): Effective or BCS permeability

Absorptive Flux

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 absorption.

Absorptive Flux

\[ \text{Absorptive Flux (J)} = C_{\text{int}} \cdot P_{\text{wall}} \]

\( P_{\text{wall}} \) = effective or BCS permeability

\( C_{\text{int}} \) = concentration in lumen

Which further implies...

When \textit{in vitro} testing can demonstrate the same GI concentration time profile under all luminal conditions....it can serve as a reliable surrogate for judging \textit{therapeutic equivalence} of pharmaceutically equivalent drug products.
Progression of IR Solid Oral Dosage Form

Dosed form must be stable in the intestinal lumen.
Correlation between Dissolution and Absorption

Defined by three dimensionless numbers

**Dose Number**

Comparison of equilibrium solubility to highest dose concentration

\[ D_0 = \frac{M_o/V_o}{C_s} \]

- \( M_o \) = dose (MW)
- \( V_o = 250 \text{ mL} \)
- \( C_s \) = equilibrium solubility

**Absorption Number**

Comparison of mean residence time to time required for absorption

\[ A_n = \frac{T_{\text{res}}}{T_{\text{abs}}} \]

- \( T_{\text{res}} \) = GI residence time
- \( T_{\text{abs}} \) = absorption time for drug substance

**Dissolution Number**

Comparison of mean residence time to time required for complete dissolution

\[ D_n = \frac{T_{\text{res}}}{T_{\text{Diss}}} \]

- \( T_{\text{res}} \) = GI residence time
- \( T_{\text{Diss}} \) = time required for dissolution of product
BCS Classification

- **Class I**: High Solubility, High Permeability
- **Class II**: High Solubility, Low Permeability
- **Class III**: Low Solubility, High Permeability
- **Class IV**: Low Solubility, Low Permeability
**BCS Class I**

- **Low \( D_0 \):** \( \downarrow M_0 \) or \( \uparrow C_s \)
  - High solubility does not limit dissolution and, therefore, absorption

- **High \( A_n \):** \( T_{abs} \) due to \( \uparrow P \)
  - High permeability ensures complete absorption within transit time

- **High \( D_n \):** \( T_{Diss} \) due to \( \uparrow DR \)
  - Rapid dissolution in relation to gastric emptying and therefore not rate limiting
In Agreement with Statement

“...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 absorption”

FDA and EMA Agree

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

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ABSORPTION SYSTEMS
“…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 absorption”

“…further implies that the two drug products have the same in vivo dissolution profile under all luminal conditions then they will have the same rate and extent of drug absorption”
EMA agrees
In Vitro Tests

- **Solubility**
  - Experimental
  - pH 1.0-7.5 or 1.2-6.8

- **Dissolution**
  - Experimental
  - 0.1 N HCl, pH 4.5 & 6.8
  - Approved Label (RLD)

- **Permeability**
  - Experimental
  - Published Literature
    - Published Clinical Data
    - Non-Clinical Data
  - Human PK
  - Non-Clinical Techniques
FDA Guidance

Guidance for Industry

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

B. Permeability

The permeability class boundary is based indirectly on the extent of absorption (fraction of dose absorbed, not systemic BA) of a drug substance in humans and directly on measurements of the rate of mass transfer across human intestinal membrane. Alternatively, nonhuman systems capable of predicting the extent of drug absorption in humans can be used (e.g., in vitro epithelial cell culture methods). In the absence of evidence suggesting instability in the gastrointestinal tract, a drug substance is considered to be highly permeable when the extent of absorption in humans is determined to be 90% or more of an administered dose based on a mass balance determination or in comparison to an intravenous reference dose.
In Other Words

High BCS (human *in vivo*) permeability = High $F_{\text{abs}}$

High *in vitro* $P_{\text{app}}$ = Always high BCS permeability

Therefore: High *in vitro* $P_{\text{app}}$ = Always high $F_{\text{abs}}$

_FDA is not aware of any cases where__ *in vitro* permeability affects the rank order relationship with the human extent of absorption…

Lawrence Yu, Director for Science, OGD. PPB Open Forum, 2010. FIP PSWC/AAPS Annual Meeting

However, High BCS permeability **not always** = high *in vitro* $P_{\text{app}}$

Residence time, Barrier differences, transporter expression etc
Question…

For a rapidly dissolving IR product with

- High permeability
- High solubility
- Adequate stability

Will absorption \textit{always} be complete?

\textbf{YES!}
FDA Experience with Biowaivers

New Drugs vs. Generics

Between 2003 – June, 2011, 54 drug products submitted to FDA for classification

Mehta, Sept. 2010; AAPS Webinar: Application of Biopharmaceutical Classification System (BCS) in Regulatory Submissions
Davit, June 2011, 'BCS Classification Workshop, Canadian Society for Pharmaceutical Sciences 'FDA Experience with Biopharmaceutics Classification System (BCS) Biowaivers
FDA Experience: Generics
Communicated via Individual Product Recommendations (IPRs)

Fed/Fasted

II. In vivo option: 2 studies

1. Type of study: Fasting
   Design: Single-dose, two-way crossover in vivo
   Strength: 15 mg
   Subjects: Healthy males and nonpregnant females, general population.
   Additional Comments:

2. Type of study: Fed
   Design: single-dose, two-way crossover in vivo
   Strength: 15 mg
   Subjects: Healthy males and nonpregnant females, general population.
   Additional comments:

Special Population

Type of study: Fasting
Design: Single-dose, two-way crossover in vivo with dosing on the first 2 days of a treatment cycle (i.e., Period I and Period II of the study are Day 1 and Day 2, respectively, of the treatment cycle)
Strength: 250 mg (dose 1x250 mg)
Subjects: Cancer patients who are already receiving or are about to start receiving temozolomide 250 mg once daily as their calculated individualized dose (e.g. based upon factors such as tumor type, body surface area, cycle number and toxicity). All subjects who received at least one dose of the investigational drug (i.e., the safety population) should be included in the assessments of safety and tolerability.
Additional Comments: Submission of an Investigational New Drug Application (IND) is required prior to conducting a bioequivalence study for a cytotoxic drug product such as temozolomide (see 21 C.F.R § 320.31).

Parent and Metabolite

Analytes to measure (in appropriate biological fluid): and its active metabolite monohydroxylated (M-II) in plasma.

Special Population with Reference Scaled Approach

Type of study: Fed
Design: Single-dose, two-way, crossover in vivo
Strength: 500 mg
Subjects: Cancer patients already receiving a stable twice-daily dosing regimen as prescribed by the reference product label (i.e. 1250 mg/m², twice daily, equivalent to 2500 mg/m² total daily dose, for two-weeks followed by a one-week rest period given as three-week cycles)
Additional Comments: See comments below:
FDA Experience: Generics
All Therapeutic Classes Considered

- Cardiac Arrhythmia: 13%
- Antibiotic: 13%
- HIV: 4%
- Cancer: 8%
- CNS: 71%
## Methods for Permeability Classification

<table>
<thead>
<tr>
<th>Direct</th>
<th>Indirect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human intestinal perfusion</td>
<td>Human PK: Absolute BA or mass balance</td>
</tr>
<tr>
<td></td>
<td>Rat intestinal perfusion</td>
</tr>
<tr>
<td></td>
<td>Epithelial cell monolayers</td>
</tr>
<tr>
<td></td>
<td>Excised human or animal intestinal tissues</td>
</tr>
</tbody>
</table>
Caco-2 Cell Monolayers

Permeability and P-gp function:
- Days in culture: 21-28
- Passage number: 58-76
- Donor pH: 6.5 and 7.4
- Multiple operators

How did you validate your test system?

\[ P_{app} = \frac{dC_1}{dt} \times \frac{v_r}{A \times C_o} \]

\[ ER = \frac{P_{app} (B \rightarrow A)}{P_{app} (A \rightarrow B)} \]
Test System Reproducibility

Permeability Values
Compound X and Minoxidil

Average $P_{app}$ ($x10^{-6}$ cm/s)

- Overall Mean 14.3
- %CV = 24.9

- Overall Mean 4.94
- %CV = 25.3

Percent Difference: Individual Study vs. Overall Mean
High Permeability Internal Standard (HPIS)

How did you choose your high permeability internal standard?

Common Issues with HPIS:
- High $P_{app}$
- Variations with donor pH
- Inaccurate classification

| HPIS     | A→B $P_{app}$ pH 6.5 (μmol/min/cm²) | A→B $P_{app}$ pH 7.4 (μmol/min/cm²) | %F
|----------|-------------------------------------|-------------------------------------|------
| Antipyrine | 63.44 ± 11.54                       | 62.54 ± 15.28                       | 100  |
| Metoprolol | 11.65 ± 1.70                        | 27.88 ± 2.80                        | 95   |
Improved HPIS

“Selection of a high permeability internal standard with permeability in close proximity to the low/high permeability class boundary may facilitate classification of a test drug substance.”
### Benefits: Accuracy

<table>
<thead>
<tr>
<th>Dose Strength</th>
<th>Concentration</th>
<th>P\textsubscript{app}</th>
<th>Recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test Compound</td>
<td>1.0 μM</td>
<td>0.95</td>
<td></td>
</tr>
<tr>
<td></td>
<td>50 μM</td>
<td>7.90</td>
<td></td>
</tr>
<tr>
<td>Dose Strength</td>
<td>3239 μM</td>
<td>N/A</td>
<td></td>
</tr>
</tbody>
</table>

**Absolute BA is 98%**

<table>
<thead>
<tr>
<th></th>
<th>P\textsubscript{app}</th>
<th>Recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test Compound</td>
<td>11.8</td>
<td>92.5%</td>
</tr>
<tr>
<td>Pindolol</td>
<td>13.9</td>
<td>96.1%</td>
</tr>
<tr>
<td>Atenolol</td>
<td>0.21</td>
<td>93.1%</td>
</tr>
</tbody>
</table>

**Pindolol is Inadequate Standard Biowaiver Recommendation in IPR**
Benefits: Covariance

Minoxidil vs. Compound X

R² = 0.68

Compound X, \( P_{\text{app}} \) (x \( 10^{-6} \) cm/s)

Minoxidil, \( P_{\text{app}} \) (x \( 10^{-6} \) cm/s)
Benefits: Normalization

Ratio of Permeability Values
Compound X over Minoxidil

Overall Mean 2.94  %CV = 14.4

Percent Difference: Individual Study vs. Overall Mean
Benefits: Regulatory Approval

At least 95% fraction absorbed

> 90% metabolized

Passive transport

No known food effects or DDI

No pH effect

How do you justify using minoxidil as your high permeability internal standard?
Multiple Validated pH Levels

Donor pH 6.5 or 7.4

<table>
<thead>
<tr>
<th>Model Compounds</th>
<th>6.5</th>
<th>7.4</th>
<th>Permeability Class</th>
<th>Fraction Absorbed (%) in Humans</th>
</tr>
</thead>
<tbody>
<tr>
<td>P_app (x10^{-9}, cm/s)</td>
<td>Recovery (%)</td>
<td>P_app (x10^{-6}, cm/s)</td>
<td>Recovery (%)</td>
<td></td>
</tr>
<tr>
<td>Antipyrine</td>
<td>63.44 ± 11.54</td>
<td>100.32 ± 4.50</td>
<td>62.54 ± 15.28</td>
<td>99.95 ± 7.77</td>
</tr>
<tr>
<td>Atenolol</td>
<td>0.19 ± 0.04</td>
<td>90.65 ± 1.79</td>
<td>0.19 ± 0.05</td>
<td>90.08 ± 7.53</td>
</tr>
<tr>
<td>Caffeine</td>
<td>45.78 ± 6.62</td>
<td>98.59 ± 2.26</td>
<td>63.61 ± 16.04</td>
<td>98.97 ± 2.14</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>40.44 ± 2.43</td>
<td>97.04 ± 2.26</td>
<td>43.04 ± 6.63</td>
<td>91.81 ± 3.52</td>
</tr>
<tr>
<td>FITC-dextran</td>
<td>&lt;0.08</td>
<td>ND</td>
<td>&lt;0.14</td>
<td>ND</td>
</tr>
<tr>
<td>Fluvastatin</td>
<td>18.56 ± 1.90</td>
<td>100.56 ± 3.00</td>
<td>5.69 ± 0.20</td>
<td>94.57 ± 8.36</td>
</tr>
<tr>
<td>Furosemide</td>
<td>0.23 ± 0.03</td>
<td>82.97 ± 1.33</td>
<td>0.18 ± 0.01</td>
<td>93.12 ± 3.33</td>
</tr>
<tr>
<td>Hydrochlorothiazide</td>
<td>0.71 ± 0.14</td>
<td>91.70 ± 3.55</td>
<td>0.55 ± 0.14</td>
<td>95.67 ± 2.42</td>
</tr>
<tr>
<td>Ketoprofen</td>
<td>60.82 ± 18.79</td>
<td>87.07 ± 2.31</td>
<td>29.25 ± 2.94</td>
<td>93.55 ± 1.31</td>
</tr>
<tr>
<td>Labetalol</td>
<td>4.04 ± 0.30</td>
<td>86.97 ± 6.32</td>
<td>13.53 ± 1.38</td>
<td>86.43 ± 3.65</td>
</tr>
<tr>
<td>Lincomycin</td>
<td>0.22 ± 0.11</td>
<td>98.62 ± 4.49</td>
<td>0.22 ± 0.09</td>
<td>82.35 ± 4.06</td>
</tr>
<tr>
<td>Mannitol</td>
<td>0.40 ± 0.02</td>
<td>96.69 ± 3.86</td>
<td>0.72 ± 0.13</td>
<td>93.45 ± 1.58</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>11.65 ± 1.70</td>
<td>94.26 ± 2.39</td>
<td>27.88 ± 2.51</td>
<td>91.52 ± 2.83</td>
</tr>
<tr>
<td>Minoxidil</td>
<td>3.11 ± 0.72</td>
<td>91.61 ± 8.80</td>
<td>2.71 ± 0.42</td>
<td>91.47 ± 6.76</td>
</tr>
<tr>
<td>Nadolol</td>
<td>0.19 ± 0.15</td>
<td>92.27 ± 3.45</td>
<td>0.32 ± 0.08</td>
<td>91.54 ± 3.77</td>
</tr>
<tr>
<td>Naproxen</td>
<td>60.33 ± 6.11</td>
<td>92.39 ± 3.15</td>
<td>59.17 ± 2.64</td>
<td>88.12 ± 0.87</td>
</tr>
<tr>
<td>Pindolol</td>
<td>4.09 ± 1.38</td>
<td>89.65 ± 4.19</td>
<td>17.00 ± 4.28</td>
<td>91.99 ± 6.81</td>
</tr>
<tr>
<td>Propranolol</td>
<td>17.99 ± 4.62</td>
<td>94.37 ± 1.56</td>
<td>31.75 ± 4.33</td>
<td>89.25 ± 1.92</td>
</tr>
<tr>
<td>Ranitidine</td>
<td>0.24 ± 0.03</td>
<td>92.10 ± 2.85</td>
<td>0.28 ± 0.04</td>
<td>91.20 ± 3.69</td>
</tr>
<tr>
<td>Sulfasalazine</td>
<td>0.08 ± 0.01</td>
<td>96.74 ± 3.42</td>
<td>0.07 ± 0.00</td>
<td>88.63 ± 2.25</td>
</tr>
<tr>
<td>Theophylline</td>
<td>32.47 ± 5.42</td>
<td>96.65 ± 2.50</td>
<td>28.70 ± 2.29</td>
<td>93.53 ± 1.83</td>
</tr>
<tr>
<td>Timolol</td>
<td>5.89 ± 2.26</td>
<td>91.22 ± 3.89</td>
<td>18.71 ± 4.87</td>
<td>94.19 ± 9.13</td>
</tr>
<tr>
<td>Verapamil</td>
<td>10.84 ± 2.32</td>
<td>106.08 ± 19.74</td>
<td>20.17 ± 1.28</td>
<td>87.57 ± 13.92</td>
</tr>
</tbody>
</table>
Obtaining Quality Permeability Data

- Mass balance
- Replicates
- Time points
- Relevant concentrations
- Lack of interactions between test compound and co-dosed controls
Mass Balance

- Underestimated $P_{app}$
- Exaggerated efflux ratio
- FDA expects >80% recovery

$$P_{app} = \frac{dC_r / dt \times V_r}{A \times C_0}$$

$$R = \frac{P_{app(B-A)}}{P_{app(A-B)}}$$

Provide intracellular accumulation data to demonstrate mass balance
Time Points

- Highly Permeable Test Compound
- Borderline Test Compound
- BCS Class I Reference Compound
- Low Control Compound
### Replicates

<table>
<thead>
<tr>
<th></th>
<th>Test Compound A-to-B $P_{app}$</th>
<th>Minoxidil A-to-B $P_{app}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study 1</td>
<td>5.89</td>
<td>5.87</td>
</tr>
<tr>
<td>Study 2</td>
<td>4.47</td>
<td>5.51</td>
</tr>
</tbody>
</table>

For a given test method with set conditions, selection of a high permeability internal standard with permeability in close proximity to the low/high permeability class boundary may facilitate classification of a test drug substance. For instance, a test drug substance may be determined to be highly permeable when its permeability value is equal to or greater than that of the selected internal standard with high permeability.
## Relevant Concentration Range

<table>
<thead>
<tr>
<th>Test Compound Concentration</th>
<th>Efflux Ratio</th>
<th>Permeability Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 µM</td>
<td>6.2</td>
<td>Similar</td>
</tr>
<tr>
<td>32 µM</td>
<td>1.9</td>
<td>High</td>
</tr>
<tr>
<td>100 µM</td>
<td>1.2</td>
<td>High</td>
</tr>
<tr>
<td>320 µM</td>
<td>0.9</td>
<td>High</td>
</tr>
</tbody>
</table>

### Consider:
- Highest dose per administration vs. highest dose strength
- Tolerability
  - Monolayer Integrity
  - pH Verification
- Analytical sensitivity
Lack of Interaction with Internal Standards

Phase 1A:
- Test compound coadministered with controls

Phase 1B:
- Test compound without controls
- PEDS

Phase 2 (GLP):
- Unidirectional coadministered with controls
- Bidirectional without controls

Does the test compound impact permeability of internal standards and vice versa?

The choice of internal standards should be based on compatibility with the test drug substance (i.e., they should not exhibit any significant physical, chemical, or permeation interactions).
Correlation: Caco-2 $P_{app}$ vs. Human $F_{abs}$
Quadrant 4: *In Vitro* Limitations

- Transporter expression
- Residence time
- Barrier differences
- Inaccurate HPIS
- NSB of drug substance
Why Quadrant 2?

Highly Variable Drugs

RMSE $> 0.3$

Consistently Inconsistent (drug substance related)
- Extensive pre-systemic metabolism

Inconsistently Inconsistent (drug product related)
- Drug release rate
Prevalence of HVDs

Therapeutic Class Independent

180 Different Drugs
ANDA Applications from 2003-2005

57 Drugs are HVDs

22 Inconsistently Inconsistent
35 Consistently Inconsistent (83% pre-systemic metabolism)

23% Metabolism

123 less variable drugs
**BE Issues**

**Flat Dose Response Curve**

- HVDs typically have flat dose response curves and large therapeutic windows
- Clinically important adverse drug reactions occur at much higher doses than required for efficacy
- Ironically they require a great number of subjects for the BE study to pass

**Biostudy**

<table>
<thead>
<tr>
<th></th>
<th>Subjects</th>
<th>Approach</th>
</tr>
</thead>
<tbody>
<tr>
<td>Highly Variable Drugs</td>
<td>55 min.</td>
<td>RSA RTR</td>
</tr>
<tr>
<td>Less Variable Drugs</td>
<td>32 max.</td>
<td>Two treatment crossover</td>
</tr>
</tbody>
</table>

Applying BCS for HVDs

$Fa$ is the fraction of the drug that is absorbed from the intestinal lumen to the intestinal enterocytes.

$Fg$ is the fraction of the unmetabolized drug in the enterocytes. $Fa \times Fg$ reaches the portal vein.

$Fh$ is the fraction of the unmetabolized drug in the liver. $Fa \times Fg \times Fh$ reaches systemic circulation.

**Bioavailability ($F\%$)** = “the rate and extent to which an active moiety becomes available in the systemic circulation.”
HVD: Extensive Metabolism, High Variability

Rapid absorption

Extensive metabolism
- 29-63% in urine
- 18-38% in feces

Plasma concentrations of unchanged drug very low and highly variable ($C_{\text{max}}$ 1 to 6 ng/mL, $t_{\text{max}}$ 40-90 min)

<table>
<thead>
<tr>
<th>BCS Permeability Data</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>$P_{\text{app}}$</td>
<td>33.6</td>
</tr>
<tr>
<td>Minoxidil</td>
<td>4.33</td>
</tr>
<tr>
<td>Atenolol</td>
<td>0.26</td>
</tr>
<tr>
<td>Efflux Ratio</td>
<td>1.1</td>
</tr>
<tr>
<td>Recovery</td>
<td>89%</td>
</tr>
</tbody>
</table>

Individual Product Recommendation (IPR)
Source: FDA Website

- Form/Route: Tablet/Oral
- Recommended studies: 2 Options: BCS or In-Vivo Studies
HVD: Analysis of Parent and Metabolite

Rapid absorption and extensive metabolism
Oral bioavailability: 1.8 %
Wide therapeutic window and flat dose effect relationship

<table>
<thead>
<tr>
<th>BCS Permeability Data</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>$P_{app}$</td>
<td>50.6</td>
</tr>
<tr>
<td>Minoxidil</td>
<td>5.33</td>
</tr>
<tr>
<td>Atenolol</td>
<td>0.40</td>
</tr>
<tr>
<td>Efflux Ratio</td>
<td>1.18</td>
</tr>
<tr>
<td>Recovery</td>
<td>101%</td>
</tr>
</tbody>
</table>

Individual Product Recommendation (IPR)
Source: FDA Website

Form/Route: Tablet/Oral
Recommended studies: 2 Options: BCS or In-Vivo Studies

BE Studies Require Parent & Metabolite to be Analyzed!
Conclusions

Well performed *in vitro* investigations can be used for pivotal classification

Caco-2 is conservative and reproducible

Minoxidil is accurate and independent of donor pH
## Global Acceptance and Experience

<table>
<thead>
<tr>
<th>Country</th>
<th>Year Issued</th>
<th>Dissolution</th>
<th>Permeability</th>
<th>Solubility</th>
</tr>
</thead>
<tbody>
<tr>
<td>USA</td>
<td>2000</td>
<td>85% in 30 min</td>
<td>90%</td>
<td>1-7.5</td>
</tr>
<tr>
<td>Europe</td>
<td>2001 (2010)</td>
<td>85% in 15 min</td>
<td>85%</td>
<td>1-6.8</td>
</tr>
<tr>
<td>ASEAN</td>
<td>2004</td>
<td>Rapid</td>
<td>High</td>
<td>1-6.8</td>
</tr>
<tr>
<td>WHO</td>
<td>2006</td>
<td>85% in 30 min</td>
<td>85%</td>
<td>1.2-6.8</td>
</tr>
<tr>
<td>ANVISA</td>
<td>2011</td>
<td>Specified List</td>
<td>85%</td>
<td>Specified List</td>
</tr>
<tr>
<td>TGA</td>
<td>2011</td>
<td>85% in 15 min</td>
<td>85%</td>
<td>1-6.8</td>
</tr>
<tr>
<td>Canada</td>
<td>2012</td>
<td>85% in 30 min</td>
<td>85%</td>
<td>1.2-6.8</td>
</tr>
</tbody>
</table>
Thank You

These slides are available at absorption.com/disso