Highly variable drugs: reasons for high variability and solutions to overcome BE problems

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Concepts in Drug Research and Development

Modern Strategies for the Development of Generic Drugs
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A very long story ...

First step: Bio-international '89
■ HVD identified as significant BE problem

Statement Prof. Lezlie Benet
“For a drug, not a narrow therapeutic index compound, with significant PK variability in BA tests the statisticians estimated that a crossover study in 162 volunteers would be requested to meet the acceptance criteria to prove bioequivalence. I suggested that such study was inappropriate …”

Milestone: Bio-international '92
■ definition of highly variable drugs
■ sources of variability
Highly variable drugs

Definition BIO-international ’92 [2001]
"Drugs which exhibit intra-subject variabilities >30 % (CVANOVA) are to be classified as highly variable ..."

Essential differentiation
- highly variable drug substances, e.g. statins
- highly variable drug products, e.g. enteric coated

Sources of (high) variability
- administration conditions, interactions with food
- physiological factors (GE, transit, first-pass, ...)
- technical aspects, e.g. bioanalytical procedures

... over more than a decade ...

Numerous international conferences
- Bio-international '94, Munich/Germany
- Bio-international '96, Tokyo/Japan
- FDA/AAPS Conference 1998, Montreal/Canada
- 1st PSWC, San Francisco/U.S.A.
- EUFEPS Conference 2002, Copenhagen/Denmark
- ...

Research initiated
- replicate design, assessing within-subject variability
- multiple dosing, significant dampening of variability
US-FDA: clear tendency
- in favour of replicate design approach
- rejection of multiple dosing as less discriminative ...

Individual BE - "a comedy of errors" (Shakespeare) ?
- "prescribability" vs. "interchangeability"
- S*F interaction – what does it mean therapeutically ?
- concept on trial for two years, then dismissed ...

Reference scaled procedure – more than a tryout ?
- widening of acceptance criteria due to scaling ...
- ... based on Reference product related variability

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The problem continues

Market experience
800 studies (s.d., fasted) evaluated in the U.S.A.

<table>
<thead>
<tr>
<th>WSV</th>
<th>failed studies (%)</th>
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<tbody>
<tr>
<td>&lt; 10%</td>
<td>6%</td>
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<tr>
<td>10-20%</td>
<td>10%</td>
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<tr>
<td>20-30%</td>
<td>26%</td>
</tr>
<tr>
<td>&gt;30%</td>
<td>62%</td>
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<table>
<thead>
<tr>
<th>number of subjects</th>
<th>failed studies (%)</th>
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<tbody>
<tr>
<td>0-12</td>
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<tr>
<td>49-60</td>
<td>68%</td>
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<tr>
<td>&gt;60</td>
<td>12%</td>
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M. Tanguay et al.: AAPS Abstract, 2002
**Ultimate rationale: widening**

Based on clinical justification
- the European approach for long time (decades) ...
- ... "deemphasised" due to various concern/difficulties

Broad support for scaling procedure
- US-FDA intended to implement Guideline
- concept:
  - replicate design BE studies for HVD
  - widening based on reference product variability

... and Europe?

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**Europe takes initiative ...**

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[Image of European Medicines Agency document]

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Concept paper and its consequences

Suggested approach: scaled average BE
- recommended study design
- appropriate acceptance range
- recommended statistical procedure
- how to proceed with WSV Test > Reference?
- handling of outliers

Paper withdrawn ... 
- insurmountable conflictive positions ...
- ... consensus not achievable

Like Phoenix from the Ashes ...

New European regulations

European Medicines Agency
London, 20 January 2010
Doc. Ref.: CPMP/QWP/1401/95 Rev. 1

COCOMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE
(COMP)

GUIDELINE ON THE INVESTIGATION OF BIOEQUIVALENCE

4.1.10 Highly variable drugs or drug products
Highly variable drug products (HVDP) are those whose intra-subject variability for a parameter is larger than 30%. If an applicant suspects that a drug product can be considered as highly variable in its rate and/or extent of absorption, a replicate cross-over design study can be carried out.
Highly variable drugs: European regulations – useful in solving problems in BE assessment?

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