IMPLEMENTATION OF NEW EU BIOEQUIVALENCE GUIDELINES
November 2010

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<table>
<thead>
<tr>
<th>COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)</th>
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</thead>
<tbody>
<tr>
<td>GUIDELINE ON THE INVESTIGATION OF BIOEQUIVALENCE</td>
</tr>
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<thead>
<tr>
<th>DISCUSSION IN THE JOINT EFFICACY AND QUALITY WORKING GROUP</th>
<th>December 1997 – October 1998</th>
</tr>
</thead>
<tbody>
<tr>
<td>REV. 1 AGREED BY THE EFFICACY WORKING PARTY</td>
<td>January 2010</td>
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<tr>
<td>REV. 1 ADOPTION BY CHMP</td>
<td>20 January 2010</td>
</tr>
<tr>
<td>REV. 1 DATE FOR COMING INTO EFFECT</td>
<td>1 August 2010</td>
</tr>
</tbody>
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The European Medicines Agency (EMA) is a Medicines Regulatory Agency of the European Union with headquarters in Canary Wharf, London.

The EMA, co-ordinates, through its scientific committees the evaluation of Marketing Authorisation Applications and liaises with individual Member States.

www.ema.europa.eu
EU Bioequivalence Guidelines

Scope - Immediate release formulations with systemic action

- Outlines when bioavailability studies not required (waver for additional strengths, specific types of formulations, biowaver)

- not – MR, transdermal, inhaled, biologicals
Design - guidance on conduct and evaluation of bioequivalence studies
- address linearity of PK
- need for fed and fasted
- Standard design: randomised 2-period 2-sequence single dose crossover design, wash out (5 elimination half lifes)
- Other options - parallel design (long half life)
- replicate design (highly variable PK)
- multiple dose in patients (tolerance and SD not feasible in Pts or analytical methods)
EU Bioequivalence Guidelines

Guidance on
- Reference and test product
  - number and selection of subjects
  - study conduct
  - standardisation – diet, fluid, exercise
  - sampling times – single dose
  - fasted vs fed vs both
Sampling Times

- Frequent sampling around predicted Tmax
- Sampling long enough to provide a reliable estimate of extent of exposure ($AUC_{(0-t)}$ covers at least 80% $AUC_{(0-\infty)}$)
- $AUC_{(0-72h)}$ may be used
- When to take: multiple dose studies
- Urine
- Covers endogenous substances
Characteristics to be investigated

- PK parameters
  - AUC (0-t)
  - AUC\(_{(0-\infty)}\)
  - Residual areas
  - Cmax
  - Tmax

- Discussion on parent or metabolite
  - In general bioequivalence should be based on parent
  - If prodrug low concentration, quickly eliminated, metabolite may be accepted

- Discussion on enantiomers
- Use of urinary data
- Correction for endogenous substance
Discussion on bioanalytical methodology

- Lower limits of quantitation
- Evaluation
- Subject accountability
- Reason for exclusion
- Parameters to be analysed
- Statistical analysis
- Carry-over effects
- Study report
Strengths to be Investigated

- May not be necessary to test all strengths depending on linearity

- PK considered linear if difference is dose adjusted mean AUC $\leq 25\%$ when compared

- If bioequivalence has been demonstrated at the strengths that are most sensitive to detect potential differences, other strengths can be waived.
Biowaiver: General Criteria: for Waiver for Additional Strengths

- Products made by same process
- Qualitative composition same
- Composition qualitatively proportional
- Appropriate in-vitro dissolution data

Generally use highest strength
Discussion on linearity & non-linear PK
Normal Acceptance Range

AUC\(_{(0-t)}\) & Cmax:

- 90% confidence intervals 80.00-125.00%

Tmax not usually required unless clinically relevant or important for onset of actions or related to AE’s

Narrow therapeutic range drugs: may need tightening: 90.00-III.II% AUC & also Cmax where relevant

For Highly variable drugs: Cmax may be widened.
Highly Variable Drugs

Intra-subject variability > 30%

If applicant suspects highly variable drug in rate or extent of absorption, a replicate cross-over design can be carried out.

Where Cmax is considered clinically irrelevant, possible to widen acceptance range to 69.84 – 143.19% but must be demonstrated in replicate design.
Biopharmaceutics Classification System (BCS) – based Biowaver

- Aim - Reduce in-vivo bioequivalence studies
  - may represent surrogate for in-vivo bioequivalence

- Restricted to highly soluble drug substance with known human absorption and considered not to have narrow therapeutic index

- Immediate release, solid forms, : NOT sublingual, buccal or MR formulation

- Bioequivalence between test and reference [whether generic, line extension, variation, trial and to be marketed products]
Biopharmaceutics Classification System (BCS) – based Biowaver

Requirements:

- Highly solubility and complete absorption (BCS-Class I)
- Very rapid (>85% within 15mm) or similarly rapid (85% within 30 minutes) in-vitro dissolution
- Excipients that might affect bioavailability are qualitatively and quantitatively the same
- Also applicable if:
  - High solubility and limit absorption (Class III) and very rapid dissolution and excipients the same
Biopharmaceutics Classification System (BCS) – based Biowaver

Special Considerations

- Different salts might be acceptable
- Different ester, ether, isomes, complex, derivative not acceptable
- Guidelines defines solubility
- Guidelines defines absorption (≥ 85%)
- Guidelines defines in-vitro dissolution
- Fixed combination products, might be acceptable if all actives belong to BCS-Class I or III)
EU Bioequivalence Guidelines: Conclusion

- Clarifies requirements for bioequivalence
- Clarifies acceptance limits
- Addresses difficult area like highly variable drugs
- Addresses what doses/studies/designs need to be investigated
- Clarifies where biowaives might be appropriate