Evaluations of the Impact of Regulatory Decisions and Scientific Principles in the BE Studies

A. Atilla Hincal, PhD
IDE Pharmaceutical Registration Biopharmaceutic Consultancy Education Ltd. Co.
Ankara Turkey

Professor Emeritus Hacettepe University
Ankara Turkey
Presentation Outline

- Introduction
- International Pharma Regulatory Related Developments
- Important aspect involved in BE and Regulatory Requirement
- Regulatory Authorities and Organizations and BE Guidelines
- Conclusion
Introduction

BIOEQUIVALENCE STUDIES

- SPONSOR
- HEALTH AUTHORITY
- SERVICES PROVIDERS
  - MANAGEMENT CRO
  - CLINICAL CRO
  - ANALYTICAL CRO

SCIENCE BASED REGULATORY AFFAIRS
<table>
<thead>
<tr>
<th>Type</th>
<th>Patent Certification</th>
<th>ANDA Filing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paragraph I</td>
<td>The drug has not been patented.</td>
<td>If a generic drug manufacturer certifies I &amp; II, then the FDA starts processing the generic ANDA right away</td>
</tr>
<tr>
<td>Paragraph II</td>
<td>The patent has already expired.</td>
<td>If a generic drug manufacturer certifies 3, then the FDA starts processing the ANDA, and gives approval when the patent expires</td>
</tr>
<tr>
<td>Paragraph III</td>
<td>The generic drug will not go on the market until the day of expiry</td>
<td></td>
</tr>
</tbody>
</table>
| Paragraph IV     | The patent is not infringed or is invalid                 | ANDA filer notifies patent holder within 20 days  
− Patent holder must sue for infringement within 45 days  
− If the patent holder sues, FDA must withhold approval for 30 months (one time only)  
− If the patent holder does not sue, FDA may approve ANDA at any time  
− If a court rules that the patent is not infringed or invalid, FDA may proceed after decision.  
− If first generic ANDA files, gets 180 days exclusivity (per product) |
Requirements for BE Studies
## Demographic Requirement

<table>
<thead>
<tr>
<th>Regulatory Agency</th>
<th>Age (year)</th>
<th>SEX</th>
<th>BMI (kg/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>U.S.A</td>
<td>18 years of age or older</td>
<td>Both sex</td>
<td>18.5 - 24.9</td>
</tr>
<tr>
<td>Europe</td>
<td>18 years of age or older</td>
<td>Both sex</td>
<td>18.5 - 30</td>
</tr>
<tr>
<td>Japan</td>
<td>Healthy adult volunteers</td>
<td>---------</td>
<td>18.5 - 25.0</td>
</tr>
<tr>
<td>Canada</td>
<td>18 to 55 older</td>
<td>Both sex</td>
<td>Height/weight ratio for healthy volunteer subjects should be within 15 percent of the normal range.</td>
</tr>
</tbody>
</table>
### Diet and fluid requirement

<table>
<thead>
<tr>
<th>Regulatory Agency</th>
<th>Diet</th>
<th>Fluid Intake</th>
</tr>
</thead>
</table>
| USA               | 1. No food should be allowed for at least 4 hours post-dose. Subjects should start the recommended meal 30 minutes prior to administration of the drug product. Study subjects should eat this meal in 30 minutes or less; however, the drug product should be administered 30 minutes after start of the meal. 2. Standardized meals scheduled at the same time in each period of the study. (US FDA BA/BE, 2003) | 1. Subjects should be administered the drug product with 240 ml (8 fluid ounces) of water.  
 ii) Water is allowed as desired except for one hour before and one hour after drug administration. |
| Europe            | i) No food is allowed for at least 4 hours post-dose. Meals taken after dosing should be standardised in regard to composition and time of administration during an adequate period of time. (fasting study)  
 ii) In fed conditions, the timing of administration of the drug product in relation to food intake is recommended to be according to the SmPC or the originator product. If no specific recommendation is given in the SmPC or in the originator product, it is recommended that subjects should start the meal 30 minutes prior to administration of the drug product and eat this meal within 30 minutes. (fed study)  
 (Europe BA/B/CPMP/EWP/QWP/1401/98 Rev. 1/Corr *) | * Test and reference products should be administered with a standardised volume of fluid (at least 150 ml).  
 * Water is allowed as desired except for one hour before and one hour after drug administration. |
| Japan             | Similar to USA  
 - If bioavailability under fasting conditions is markedly low, or a high incidence of severe adverse effects is indicated, drugs may be given postprandially. For a postprandial dose, the meal should be eaten within 15 minutes, and the drug administered according to the dosing regimen or 30 minutes (NIHS Japan, 2000) | Similar to Europe |
| Canada            | Similar to Europe  
 - All meals should be standardized and repeated on each study day.  
 (HPB BA/BE, 2009) | 1) Similar to Europe  
 2) When comparing the performance of two orally disintegrating dosage forms that are intended to be taken without water, the comparative bioavailability study should be designed to challenge the formulation under the most discriminatory conditions. For such dosage formulations, water should not be administered from one hour prior to dosing and up to one hour post-dosing. |
## Fasting requirement

<table>
<thead>
<tr>
<th>Regulatory Agency</th>
<th>Fasting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Europe</td>
<td>At least 8 hours prior to administration of the products and no food is allowed for at least 4 hours post-dose.</td>
</tr>
<tr>
<td>U.S.A</td>
<td></td>
</tr>
<tr>
<td>Canada</td>
<td>At least 10 hours of fasting which is continued for at least 4 hours post-dose.</td>
</tr>
<tr>
<td>Japan</td>
<td></td>
</tr>
</tbody>
</table>
Fed study Requirement

- **Meal should contain for Fed BE study**
  
  **US, Europe, AU:**
  - high fat-high caloric meal.
  - Fat 50% of total caloric content of the meal
  - 800-1000 calories considered as high calories.

- **Meal should contain**
  
  **US, Europe, AU:**
  - 150 cal. protein, 250 cal. Carbohydrates, 500-600 cal. fat.

  **Japanese NIHS:**
  - low fat and high caloric food
  - The caloric content is app 700 kcal. Not more than 20% (140 kcal) is derived from the fat.
## Sample size

<table>
<thead>
<tr>
<th>Regulatory Agency</th>
<th>Minimum</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>U.S.A</td>
<td>12</td>
<td>The total number of subject in the study should provide adequate power for BE demonstration.</td>
</tr>
<tr>
<td>Europe</td>
<td>12</td>
<td>Not Specified in BE Guideline, ICH E9 section 3.5 applies which state 'The number of subject in clinical trial should always large enough to provide a reliable answer to the question addressed'</td>
</tr>
<tr>
<td>Canada</td>
<td>12</td>
<td>Not Specified in BE Guideline</td>
</tr>
<tr>
<td>Japan</td>
<td>20</td>
<td>Not Specified in BE Guideline</td>
</tr>
</tbody>
</table>
## Add on design

<table>
<thead>
<tr>
<th>Regulatory Agency</th>
<th>Add on</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Europe</strong></td>
<td>It is acceptable to use a two-stage approach when attempting to demonstrate bioequivalence. An initial group of subjects can be treated and their data analysed. If bioequivalence has not been demonstrated an additional group can be recruited and the results from both groups combined in a final analysis. If this approach is adopted appropriate steps must be taken to preserve the overall type I error of the experiment and the stopping criteria should be clearly defined prior to the study. The analysis of the first stage data should be treated as an interim analysis and both analyses conducted at adjusted significance levels. (Europe BA/BE CPMP/ EWP/QWP/1401/98 Rev. 1/ Corr *).</td>
</tr>
<tr>
<td><strong>Japan</strong></td>
<td>Also for add on study additional 10 subjects are recommended along with initial subjects</td>
</tr>
<tr>
<td><strong>Canada</strong></td>
<td>As a result of random variation or a larger than expected relative difference, there is no guarantee that the sample size as calculated will pass the standards. If the study is run with the appropriate size and the standards are not met, the sponsor may add more subjects (a minimum of 12). The same protocol should be used (i.e., same formulations, same lots, same blood sampling times, a minimum number of 12 subjects, etc.). The choice to use this strategy, as with all designs, should be declared and justified a priori. The level of confidence should be adjusted using the Bonferroni procedure. The t-value should be that for p=.025 instead of .05. (HPB BA/BE Canada, 2009)</td>
</tr>
<tr>
<td>Regulatory Agency</td>
<td>Immediate Release</td>
</tr>
<tr>
<td>-------------------</td>
<td>-------------------</td>
</tr>
</tbody>
</table>
| **U.S.A**         | Total of 2 studies:  
1 single dose crossover study  
fasted 1 single dose crossover study, fed*  
* If food mentioned in the product  
Monograph if a multiple-dose study design is important, appropriate dosage administration and sampling be carried out to document attainment of steady state. | Fasting and fed  
If a multiple-dose study design is important, appropriate dosage administration and sampling be carried out to document attainment of steady state. |
| **Europe**        | Total of 1-2 studies:  
1 single dose crossover study, Fasted.  
OR  
Fed condition according to SmPC  
Recommendations related with food interaction effects.  
(Europe BA/BE CPMP/EWP/QWP/1401/98 Rev. 1/ Corr *). | Fasting, fed and steady state |
| **Japan**         | Fasting and fed    | Fasting, fed and steady state |
| **Canada**        | Fasting           | Fasting and fed  
If Steady-state studies are required, the food and fluid conditions and restrictions noted above should apply on the preceding evening and on the day the plasma profiles are to be obtained. (HPB BA/BE Canada, 2009). |
### Strength to be investigated

<table>
<thead>
<tr>
<th>Regulatory Agency</th>
<th>Linear Pharmacokinetics</th>
<th>Non Linear Pharmacokinetics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Europe</td>
<td>The bioequivalence study should in general be conducted at the highest strength</td>
<td>1. For drugs with non-linear pharmacokinetics characterized by a more than proportional increase in AUC with increasing dose over the therapeutic dose range, the bioequivalence study should in general be conducted at the highest strength. As for drugs with linear pharmacokinetics a lower strength may be justified if the highest strength cannot be administered to healthy volunteers for safety/tolerability reasons. Likewise a higher dose may be used in case of sensitivity problems of the analytical method in line with the recommendations given for products with linear pharmacokinetics above.</td>
</tr>
<tr>
<td></td>
<td>Highly soluble drug and any safety concern. Lower strength acceptable</td>
<td>2. For drugs with a less than proportional increase in AUC with increasing dose over the therapeutic dose range, bioequivalence should in most cases be established both at the highest strength and at the lowest strength (or strength in the linear range). i.e. in this situation two bioequivalence studies are needed.</td>
</tr>
<tr>
<td></td>
<td>Problems of sensitivity of the analytical method: Highest strength acceptable</td>
<td>If the non-linearity is not caused by limited solubility but is due to e.g. saturation of uptake transporters and provided that a) same manufacturing process b) Qualitative composition of the different strengths is the same c) composition of the strengths are quantitatively proportional d) appropriate in vitro dissolution data should confirm the adequacy of waiving additional in vivo</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bioequivalence testing and the test and reference products do not contain any excipients that may affect gastrointestinal motility or transport Protein, it is sufficient to demonstrate bioequivalence sport proteins at the lowest strength (or strength in the linear range). (Europe BA/BE CPMP/EWP/ QWP/1401/06 Rev. 1/ Corr “).</td>
</tr>
<tr>
<td>U.S.A.</td>
<td>Reference Listed Drug (RLD) in the Orange Book*</td>
<td>Not addressed in Guidances. Refer to Reference Listed Drug (RLD) in the Orange Book</td>
</tr>
<tr>
<td></td>
<td>*usually the highest strength if formulations are proportionally similar</td>
<td></td>
</tr>
<tr>
<td>Canada</td>
<td>Use strength with largest sensitivity to identify differences in formulation</td>
<td></td>
</tr>
</tbody>
</table>

*ILAC: INFORMATION MANAGEMENT EDUCATION*
### Acceptance criteria for bioequivalence

<table>
<thead>
<tr>
<th>Regulatory Agency</th>
<th>90% confidence interval on Log transformed data</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$C_{max}$</td>
</tr>
<tr>
<td>U.S A.</td>
<td>80-125</td>
</tr>
<tr>
<td>Europe &amp; Australia</td>
<td>80-125</td>
</tr>
</tbody>
</table>

- **Japan:**
  1. The total sample size of the initial bioequivalence study is not less than 20 (n=10/group) or pooled sample size of the initial and add-on subject studies is not less than 30.
  2. The differences in average values of logarithmic AUC and $C_{max}$ between two products are between $\log(0.9) - \log(1.11)$.
  3. Dissolution rates of test and reference products are evaluated to be equivalent as per dissolution test. The dissolution characteristics of the test product must be similar to those of the reference product under all of the following conditions when dissolution tests are performed according to the dissolution tests for oral conventional dosage forms and enteric coated products. Either the rotating basket or disintegration testing apparatus can be selected, the reason for which should be stated. The testing times are 2hr in pH 1.2 medium and 24 hr in other test fluids. The test can be ended at the time when the average dissolution of reference product reaches 85%. However, the 3rd rule can not be applied to slowly dissolving products from which more than 80% of a drug does not dissolve within the final testing time (2hr in pH 1.2 medium and 6 hr in others) under any conditions of the dissolution tests described in Sec.3 A.V. of Japan guideline.

- **Canada:**
  Ratio must be between 80-125. Need to pass also on potency corrected data. Add-on studies may be allowed if intra - CV greater than expected. 80-125 | Not Applicable |
## Acceptance criteria for bioequivalence for special class drug

<table>
<thead>
<tr>
<th>Regulatory Agency</th>
<th>Narrow therapeutic index drugs</th>
<th>Highly variable drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>90% confidence interval</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Log transformed data</td>
<td></td>
</tr>
<tr>
<td></td>
<td>$C_{\text{max}}$</td>
<td>$AUC_{\text{tr}}$</td>
</tr>
<tr>
<td>U.S.A</td>
<td>80-125</td>
<td>80-125</td>
</tr>
<tr>
<td>Europe</td>
<td>90.00-111.11</td>
<td>90.00-111.11</td>
</tr>
<tr>
<td>Japan</td>
<td>90.00-111.11</td>
<td></td>
</tr>
<tr>
<td>Canada</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saudi Arabia</td>
<td>90-111</td>
<td></td>
</tr>
<tr>
<td>ASEAN</td>
<td>acceptance interval may need to be tightened</td>
<td>acceptance interval may need to be tightened</td>
</tr>
</tbody>
</table>
International Generic Drug Regulators Programme (IGDRP)

- increasing the efficiency of review procedures;
- strengthening the regulatory review process and human resource capacity;
- applying an appropriate level of global regulatory oversight through information exchange and coordination, while reducing unnecessary regulatory burden; and
- promoting the adoption of modern science and risk based approaches on the part of both industry and agencies.
IGDRP

Benefits to a collaborative generic review process

WHO Drug Information Vol. 28 No. 1, 2014 Regulatory harmonization

- Improved operational efficiencies
- Potentially faster and more consistent review and approval process
- Greater availability of generics that may otherwise not be registered in certain markets
- Regulatory convergence, promotion of regulatory science and the strengthening of RAs
- Greater regulatory oversight and peer review
- Reduction in overall regulatory burden and less duplication of effort
- Lower regulatory and product development costs/times
- Greater alignment of industry submission practices
- Fewer parallel registrations
- More affordable generic medicines
- Mutual learning and consistency in applying international guidelines such as ICH Q8(R2)
Challenges to a collaborative generic review process

WHO Drug Information Vol. 28 No. 1, 2014 Regulatory harmonization

- Unfamiliarity with regulatory systems of other RAs
- Differences in:
  - Legal frameworks: definitions of terms (“generic”, “reference product”, “data exclusivity”, “pharmacopoeia”, “variations”, etc.)
  - Treatment guidelines/therapeutic traditions between countries, both in terms of the medicines acceptable for market authorizations by RAs and acceptable indications
  - Technical requirements, e.g. bioequivalence (BE) requirements for complex products
  - Product and active pharmaceutical ingredients (API) differences – source, method of manufacture, packaging, etc.
  - Assessment timelines, which may be anchored in regulations
  - Timing of applications due to differences in data exclusivity/patent rules
- Divergence following joint approval due to separate handling of post-approval changes
- Culture change
- Potential reduction in number of manufacturing sites, impacting on supply
- Complexity of setting up and maintaining a collaborative review system
Enablers to a collaborative generic review process

WHO Drug Information Vol. 28 No. 1, 2014 Regulatory harmonization

- Regulatory gap analysis
- Secure electronic platform for sharing of reports/comments
- Confidentiality arrangements between RAs and/or consent of applicants
- Common technical requirements and definitions
- Practices to enable filing of common dossiers:
  - Identify sections of CTD where content is identical or consolidated (e.g. Multiple pharmacopoeial references)
  - Allow different BE studies within a single application where use of different reference products is unavoidable
- Staff exchange, workshops and training
- Pilot programme, guided by policies, procedures to manage the pilot
- Leveraging the experience of Health Authorities and models such as EU and WHO
## Bioequivalence guidelines, effective dates, responsible regulatory authorities/bodies of some countries and organizations

<table>
<thead>
<tr>
<th>Country or Organization</th>
<th>BE guideline(s) referenced</th>
<th>Date posted</th>
</tr>
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</table>
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<tr>
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<tbody>
<tr>
<td>Brazil ANVISA</td>
<td>* Guide for Relative BA/BE Tests of Medicines</td>
<td>* 05.2003</td>
</tr>
<tr>
<td>Canada HC</td>
<td>* Comparative BA Standards: Formulations Used for Systemic Effects</td>
<td>* 05. 2012</td>
</tr>
<tr>
<td></td>
<td>* Conduct and Analysis of Comparative BA Studies</td>
<td>05. 2012</td>
</tr>
<tr>
<td></td>
<td>BCS Biowaiver (Draft)</td>
<td>* 08.2012</td>
</tr>
</tbody>
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</thead>
<tbody>
<tr>
<td>China SFDA</td>
<td>* Bioavailability and Bioequivalence Studies for Chemical Drug Products</td>
<td>* 03.2005</td>
</tr>
<tr>
<td>Taiwan TFDA</td>
<td>* Guideline on BA/BE Studies</td>
<td>* 04.2009</td>
</tr>
<tr>
<td>EU EMA</td>
<td>* Guideline on the Investigation of BE Note for Guidance on MR Oral and Transdermal Dosage Forms</td>
<td>01.2010</td>
</tr>
<tr>
<td></td>
<td></td>
<td>07.1999</td>
</tr>
</tbody>
</table>
### Bioequivalence guidelines, effective dates responsible regulatory authorities/bodies of some countries and organizations

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<tr>
<th>Country or Organization</th>
<th>BE guideline(s) referenced</th>
<th>Date posted</th>
</tr>
</thead>
</table>
| Mexico COFEPRIS         | * Guidelines for Submission of Research Protocols to Demonstrate the Drug Interchangeability  
|                         |                                             | * 10.2012   |
**Bioequivalence guidelines, effective dates, responsible regulatory authorities/bodies of some countries and organizations**

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<tr>
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</thead>
<tbody>
<tr>
<td>Singapore HSA</td>
<td>Follows the Association of Southeast Asian Nations (ASEAN) Guidelines for the Conduct of Bioavailability and Bioequivalence Studies</td>
<td>* 07.2004</td>
</tr>
<tr>
<td>South Korea KFDA</td>
<td>Guidance Document for Bioequivalence Study</td>
<td>* 12.2008</td>
</tr>
</tbody>
</table>
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</table>
| United Nations WHO              | * Multisource Generic Pharmaceutical Products: Guideline on Registration Requirements to Establish Interchangeability (Draft Revision)  
                                    * General Notes on Biopharmaceutic Classification System (BCS)-Based Biowaiver Applications                                                                                                                                | 10.2005      |
| United States of America FDA    | * BA & BE Studies for Orally Administered Drug Products—General Considerations  
                                    * Food-Effect BA & Fed BE Studies  
                                    * Waivers of In Vivo BA & BE Studies for IR Solid Oral Dosage Forms Based on a BCS System  
                                    * BERecommendations for Specific Products                                                                                                                                                                                                 | 03. 2003  
                                    | 01.2003  
                                    | 08.2000  
                                    | 06. 2010  |
Source Informations in Various Regulatory Agencies BE Guidelines

- Definitions of a generic and reference product
- Study design
- PK parameter calculations and BE acceptance limits
- Highly variable (HV) drugs
- Narrow therapeutic index (NTI) drugs and Critical dose drugs
- Situations in which biowaivers are granted
- Use of the BCS for granting biowaivers.
Similarities and Differences in Different BE Guidelines: Generic and Reference Product

Number of units of test product to be manufactured for the bioequivalence study

- **Similarities:**
  - Most specify a minimum test product batch size

- **Differences:**
  - **Australia, Canada, Taiwan, EMA, USA, Switzerland, WHO:**
    - a minimum of 10% of the commercial batch size or 100,000 units, whichever is greater
  - **Brazil, Singapore/ASEAN:**
    - Not specified
Similarities and Differences in Different BE Guidelines: Generic and Reference Product

• **China:**
  - a scaled-up batch or a full production batch

• **Japan:**
  - to use a lot manufactured at the same lot size as the full-scale production.
  - a lot manufactured at a scale of not less than 1/10 of a full-scale production.

• **South Korea:**
  - At least 100,000 units.
Reference product information responsible regulatory authorities/bodies of some countries and organizations

<table>
<thead>
<tr>
<th>Country or Org</th>
<th>Reference innovator product</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Australia</strong> TGA</td>
<td>The TGA prefers that the proposed generic product reference a leading brand product purchased within Australia. When justified by appropriate in vitro comparative studies, the TGA will accept BE studies where the innovator drug product was sourced from outside of Australia, although this approach is not permitted for certain types of drug substances, such as NTI drugs, drugs with complex or nonlinear kinetics and HV drugs</td>
</tr>
<tr>
<td><strong>Brazil</strong> ANVISA</td>
<td>The reference product must be registered at ANVISA, supported by documentation related to its safety, efficacy, and quality, and it must be sold in the Brazilian market</td>
</tr>
</tbody>
</table>
### Reference product information responsible regulatory authorities/bodies of some countries and organizations

<table>
<thead>
<tr>
<th>Country or org</th>
<th>Reference innovator product</th>
</tr>
</thead>
</table>
| Canada HC     | (A) A drug product in respect of which a notice of compliance is issue in pursuant with Canadian regulations and which is marketed in Canada by the innovator of the drug  
(B) A drug product, acceptable to the Minister of Health, that can be used for the purposes of demonstrating BE on the basis of pharmaceutical and. Where applicable, bioavailability characteristic, where a drug in respect of which a notice of compliance has been issued in pursuant with the Canadian regulations cannot be used for that purpose because it is no longer marketed in Canada. |
**Reference product information responsible regulatory authorities/bodies of some countries and organizations**

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<tr>
<td>Canada HC</td>
<td>regulations cannot be used for that purpose because it is no longer marketed in Canada. (C) A drug product, that is acceptable to the Minister (of Health) that can be used for the purpose of demonstrating bioequivalence on the basis of the pharmaceutical and. Where applicable, bioavailability characteristics, in comparison to a drug referred according to their regulations</td>
</tr>
</tbody>
</table>
Reference product information responsible regulatory authorities/bodies of some countries and organizations

<table>
<thead>
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<th>Reference innovator product</th>
</tr>
</thead>
<tbody>
<tr>
<td>China SFDA</td>
<td>The corresponding innovator’s drug product or the major market corresponding drug product</td>
</tr>
<tr>
<td>Taiwan TFDA</td>
<td>Generally the innovator drug product marketed in Taiwan, or the first approval drug product in Taiwan</td>
</tr>
</tbody>
</table>
| EU EMA                  | * A drug product whose marketing authorization in the EU has been granted on the basis of a complete dossier  
* If there are several dosage forms of this medicinal product on the market, the reference should be the dosage form used for the initial approval of the concerned medicinal product and which was used in the clinical efficacy and safety studies (if available) |
### Reference product information responsible regulatory authorities/bodies of some countries and organizations

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<thead>
<tr>
<th>Country or Organization</th>
<th>Reference innovator product</th>
</tr>
</thead>
<tbody>
<tr>
<td>Japan</td>
<td>A drug product that has been approved as a new drug, or a drug that corresponds to one.</td>
</tr>
<tr>
<td>Mexico COFEPRIS</td>
<td>A drug product that was registered with the Ministry of Health, which is available commercially and that is selected pursuant to the criteria established in the official regulations.</td>
</tr>
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<tr>
<td>Singapor HSA</td>
<td>An innovator drug product, which is a drug product that is authorized and marketed on the basis of a full dossier, i.e., including chemical, biological, pharmaceutical, pharmacological–toxicological and clinical data</td>
</tr>
<tr>
<td>South Korea KFDA</td>
<td>A drug that is approved (or an approved imported drug product) the safety and efficacy of which has been established or recognized by the Commissioner of the Korea FDA</td>
</tr>
<tr>
<td>Switzerland SwissMedic</td>
<td>The original product which is authorized in Switzerland, or A product registered outside of Switzerland, provided that it meets criteria for proving comparability to the original Swiss product.</td>
</tr>
</tbody>
</table>
**Reference product information responsible regulatory authorities/bodies of some countries and organizations**

<table>
<thead>
<tr>
<th>Country or organization</th>
<th>Reference innovator product</th>
</tr>
</thead>
<tbody>
<tr>
<td>United Nations WHO</td>
<td>A reference listed drug means the listed drug identified by the FDA as the drug product upon which an applicant relies in seeking approval of its ANDA</td>
</tr>
<tr>
<td>United States of America</td>
<td>A drug product that is usually the first authorized for marketing (normally as a patented product) on the basis of documentation of efficacy, safety and quality (according to the requirements at the time of authorization)</td>
</tr>
</tbody>
</table>
Similarities

All recommend the following BE study designs:
* The standard study design is a two-period crossover, in which each subject is given the test and reference formulations;
* Replicated crossover designs may also be used; and
* Parallel designs may be used for long half-life drugs
Similarities and Differences in Different BE Guidelines: General BE Study Design

Subjects

Similarities
All request healthy normal subjects, unless, for reasons of safety, it becomes necessary to use patients

Differences
Japan: subjects with low gastric acidity; in cases where
(1) the use of the drug is not limited to a specific population;
(2) the T&R products show a significant difference in (in vitro) dissolution at around pH 6.8, or between pH 3.0–6.8 for basic drugs.
This rule is not applied to enteric-coated products
Similarities and Differences in Different BE Guidelines: General BE Study Design

Age range

Similarities
All specify that studies should be conducted in adults

Differences

Brazil: 18–50
Canada, Mexico, Singapore/ASEAN, WHO: 18–55
China: 18–40
Taiwan, Japan: Healthy adults
EMA, USA: At least 18 years of age
South Korea: 19–55
USA: At least 18 years of age, and; if the drug product is to be used primarily in the elderly, the study should include as many subjects as possible of 60 years of age or older
Similarities and Differences in Different BE Guidelines: General BE Study Design

Body weight restrictions

- **Similarities**
  - All specify a body weight range, with variations listed below

- **Differences**
  - **Brazil**: body weight should be ±15% of the weight considered normal for men and women, taking into account height and physical structure
  - **Canada, EMA, Singapore/ASEAN**: Body Mass Index (BMI) within 18.5 and 30 kg/m²
  - **China**: within the normal range according to accepted normal values for BMI; avoid high variances in subjects’ body weights
  - **Taiwan**: consideration of demographic attributes of a healthy normal adult population

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Similarities and Differences in Different BE Guidelines: General BE Study Design

Body weight restrictions

- **Differences cont’d**
- **Japan**: Not specified
- **Mexico**: body weight should be no different than ±10% of the weight
- **South Korea**: a medical doctor should consider the age and health condition of the subjects
- **USA**: individuals representative of the general population
- **WHO**: weight within an acceptable range according to accepted life tables
Similarities and Differences in Different BE Guidelines: General BE Study Design

Gender, ethnicity

**Similarities**
Females.ence studies should not be pregnant

**Differences**

**Brazil**: depending on the drug product, the same number of males and females, to be distributed equally between the sequences

**China**: in general, it is recommended to recruit healthy male subjects. The study population should be determined based on the specific situation for each drug product; if female subjects are recruited they should not be pregnant

**EMA, Canada, Chinese Taipei, Singapore/ASEAN, South Korea, USA, WHO**: Subjects can belong to either sex

**Japan**: no mention other than healthy adult subjects

**Mexico**: use subjects of one sex to avoid gender-related pharmacokinetic differences
Similarities and Differences in Different BE Guidelines: General BE Study Design

Number of subjects

- **Similarities**
  - All request a minimum of 12 subjects, with the exception of the Health Authorities

- **Differences**
  - **China**: 18–24
  - **Japan**: a sufficient number to show BE
  - **Mexico**: 24 unless scientifically justified
Similarities and Differences in Different BE Guidelines: General BE Study Design

Genotyping or phenotyping

Similarities
All either
• do not mention; or
• recommend for safety or pharmacokinetic reasons

Differences
Brazil, Canada, Japan, Mexico, South Korea, USA: Not mentioned
China, EMA, Singapore/ASEAN, WHO: Consider for safety or pharmacokinetic reasons
Similarities and Differences in Different BE Guidelines: General BE Study Design

Dose strength used in the in vivo studies

**Similarities**
All recommend that generally in vivo studies should be performed on the highest strength, unless reasons of safety justify use of a lower strength

**Differences**
Some Health Authorities specify which strength should be used for drugs with nonlinear PK over the clinical dosing range

**Australia**: imposes the following restrictions on BE studies of generic drugs with non-linear or complex PK
Only a drug product marketed in Australia is acceptable as the reference
Dose strength used in the in vivo studies

- Differences

- Once this criterion is met, follow the recommendations in the EMA Guidelines.

- Canada, EMA: the strength to be used depends upon the type of nonlinearity and the underlying causes.

- If the nonlinearity is characterized by greater than proportional increases in AUC with increasing dose, conduct the BE studies on at least the highest strength.

- If the nonlinearity is characterized by less than proportional increases in AUC with increasing dose and results from saturable absorption, conduct the in vivo studies on the lowest strength.
Similarities and Differences in Different BE Guidelines: General BE Study Design

Dose strength used in the in vivo studies - 3

- **Differences**
- If the nonlinearity is reflected as less than proportional increases in AUC with increasing dose due to limited solubility of the active pharmaceutical ingredient, conduct in vivo studies on two strengths.
- **Canada** requests a fasting study on the lowest strength and a fasting and fed study on the highest strength.
- **EMA** requests a fasting and fed study on one strength and a fasting or fed study (justified based on previous knowledge and PK) on a second strength; the second strength should be the one most sensitive to detect a difference between products.
Similarities and Differences in Different BE Guidelines: General BE Study Design

Dose strength used in the in vivo studies -4

- **Differences**

  - **USA**: the strength to be used depends upon the type of nonlinearity.

  - If the nonlinearity is characterized by greater than proportional increases in AUC with increasing dose, conduct the BE studies on at least the highest therapeutic dose.

  - If the nonlinearity is characterized by less than proportional increases in AUC with increasing dose and results from saturable absorption, conduct the in vivo studies on the lowest strength.

  - **WHO**: Generally the marketed strength with the greatest sensitivity to BE assessment should be administered as a single unit.
Similarities and Differences in Different BE Guidelines: General BE Study Design

Analytes to be measured in biological fluids-1

- **Similarities**
  - Measuring and requiring the parent drug to meet BE limits unless the parent cannot be reliably measured; and
  - Measuring and requiring the major metabolite(s) to meet BE limits when the parent cannot be reliably measured

- **Differences**
  - Some provide additional reasons for measuring metabolites in biological fluids, and differ in recommending how test and reference metabolite concentrations should be statistically compared,
  - **Brazil**: measure and perform BE testing on metabolites which are formed primarily by pre-systemic metabolism;
  - Contribute meaningfully to safety and efficacy
Similarities and Differences in Different BE Guidelines: General BE Study Design

Analytes to be measured in biological fluids-2

- **Differences**

- **Canada**: quantification of metabolite levels may sometimes be helpful; for example, to explain extreme values caused by metabolite changes within a subject.

- **EMA**: using the metabolite as a surrogate for an active parent drug is expected to be accepted only in exceptional cases;

- the applicant should present any available data supporting the view that the metabolite exposure reflects parent drug metabolite formation is not saturated at therapeutic doses.
Similarities and Differences in Different BE Guidelines: General BE Study Design

Analytes to be measured in biological fluids:

- **Differences**
- **Japan**: Major active metabolites may be measured instead of the unchanged active ingredient, if it is rational.
- **Singapore/ASEAN**: With justification, BE determination can be based on metabolites when the metabolite significantly contribute to the net activity; and
- The pharmacokinetic system is non-linear.
- **South Korea**: measure and perform BE testing on active metabolites.

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Similarities and Differences in Different BE Guidelines: General BE Study Design

Analytes to be measured in biological fluids-4

- Differences

- **USA**: perform summary statistics only and use as supportive data when metabolites are formed primarily by pre-systemic metabolism; and
- Contribute meaningfully to safety and efficacy.
- **WHO**: measure and perform BE testing on metabolites when
  - The parent is a pro-drug; or
  - The metabolites are formed primarily by pre-systemic metabolism and contribute meaningfully to safety and efficacy
Similarities and Differences in Different BE Guidelines: General BE Study Design

Add-on, group-sequential, adaptive designs-1

Similarities
• Very few Health Authorities/Organizations recommend these types of designs
• Group-sequential and adaptive designs are recommended when the proposed estimate of the within-subject variability has large uncertainty.
• In a group-sequential design The overall Type I error and stopping criteria are clearly defined prior to starting the study; and
• The analysis of the first stage is treated as an interim analysis and both analyses are conducted at adjusted significance levels in an adaptive design,
• the second state sample size is based on the estimated within-subject variance from the first stage
Similarities

• “Add-on” or “additional” studies are recommended when the first (preceding) study fails to meet BE limits.

In an appropriately designed add-on or additional study, data from the preceding BE study and add-on or additional study may be combined for statistical analysis, provided that only one add-on or additional study is conducted;

• The add-on or additional study uses the same protocol as the preceding study;

• There are no fundamental differences between the first (preceding) BE study and add-on study with respect to formulation, design, and subjects; and

* The number of subjects to be included in the add-on or additional study is restricted.
Similarities and Differences in Different BE Guidelines: General BE Study Design

Add-on, group-sequential, adaptive designs

- **Differences**
- **Australia**: the most conservative of the approaches proposed in the literature, the Bonferroni correction, should be applied. This corresponds to the calculation of 95%, rather than 90%, confidence intervals
- **Brazil, China, Taiwan, Mexico, Singapore/ASEAN, WHO**: do not mention/specify
- **Canada** will accept a two-stage group-sequential BE study, provided that the plan to use a two-stage approach and adjusted significance levels is pre-defined in the protocol
- Recommends that the same alpha of 0.0294 be used for both stages
Similarities and Differences in Different BE Guidelines: General BE Study Design

Add-on, group-sequential, adaptive designs-4

- **Differences**
- **Canada, USA**: will accept a two-stage adaptive design BE study, provided that the intent to use the approach is predefined in the protocol.
- **EMA**: will accept two-stage group-sequential design BE studies, provided that the plan to use a two-stage approach and adjusted significance levels is predefined in the protocol.
- **Japan**: will accept add-on studies, provided that not less than half the number of subjects in the initial study can be added-on; the “study” is added to the statistical model as a source of variation.
Similarities and Differences in Different BE Guidelines: General BE Study Design

Add-on, group-sequential, adaptive designs-5

- **Differences**
- **USA:** will accept two-stage group-sequential design (40–43) BE studies, provided that the plan to use a two-stage approach and adjusted significance levels is predefined in the protocol.

- **South Korea** will accept an additional trial; provided that:
  - The additional trial uses at least 12 subjects per group.
  - The ratio of the mean square error from the ANOVAs of the preceding BE study and the additional trial should be smaller than the top 5% of an F-distribution with a corresponding degree of freedom; and
  - The protocol should clearly state that additional trials were conducted.

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CONCLUSION

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Most important parameters in the success of BE studies

- Sponsors / Regulatory Authorities / Service providers (CROs for Management, Clinical and Bioanalytical)
- Interpretation differences between the various guidelines,
- Interpretation differences between the members of BE commissions’s members of different countries
- Differences between the subsequent versions of the guidelines
Most important parameters in the success of BE studies

- **Sponsors / Regulatory Authorities / Service providers (CROs for Management, Clinical and Bioanalytical)**
  - Respect and follow to the international and national guidelines
  - Good knowledge level for the Formulation development and parameters, PK, PD, BE, Bioanalysis, Statistics studies and applications and project management
  - Scientific and regulatory staff expertise level must be taken into account
  - Right decisions based on the science based regulatory affairs to solve the problems and make necessary steps.
No one is perfect, that’s why pencils have erasers.

BUT DO NOT FORGET TO BE A REGULATORY EXPERT IN A FIELD AS “BE” IS NOT AN EASY TASK. IT REQUIRES SCIENTIFIC KNOWLEDGE, EXPERIENCE AND RESPECT TO THE RELATED LAWS, GUIDELINE AND HUMAN RIGHTS WHILE RUNNING A CLINICAL BE STUDY.
References

Thank you for your attention!

atilla.hincal@ide-cso.com

www.ide-cso.com