Where are we going with Dissolution and BE Studies?

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Global harmonization?

Guidelines still differ between countries / regions.

- The Network on Bioavailability and Biopharmaceutics (BABP) of the EUFEPS started the Global Bioequivalence Harmonisation Initiative (GBHI) with two conference so far (March 2015, Amsterdam and September 2016, Rockville in collaboration with the AAPS).
- The International Council on Harmonisation (ICH) recently started to focus on BE and related areas.
  - M9: Biopharmaceutics Classification System-based Biowaivers
    - Concept Paper published in October 2016.
    - Step 2 planned for 1–2Q 2018, Step 4 planned for 2Q 2019.
  - M10: Bioanalytical Method Validation
    - Concept Paper published in October 2016.
    - Step 2 planned for 2Q 2018, Step 4 planned for 2Q 2019.
  - In June 2016 the International Generic and Biosimilars Medicines Association (IGBA) joined ICH as an Assembly Member.

Global harmonization?

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- Even if one day in the (distant?) future we reach global harmonization,
  - it could only harmonize the *technical* details (designs, bioanalytical standards, statistics, protocols / reports).
    - As long as regions require the *local* reference product in BE, *e.g.*,
      USA: Reference Listed Drug
      EEA: Reference medicinal product […] on the basis of a complete dossier according to Article 8(3), 10a, 10b or 10c of 2001/83/EC,

      the *number* of studies could not decrease.
    - The WHO is having a hard time to establish a 'Global Comparator' for more than 15 years.
      - » Most innovators are reluctant to disclose which *particular* formulation (*i.e.*, marketed in *which* country) underwent the least manufacturing changes (and therefore, is expected to be the 'closest' to the phase III studies which served in the original approval).

Test and reference products

Requirements still differ between countries / regions.

Region	Generic drug	Reference product
EMA	A product that contains the same qualitatively (Q1) and quantitatively (Q2) composition in active substances, having the same pharmaceutical form as the reference product. Different salts, esters, ethers, isomers, mixtures of isomers, complexes or derivatives of an active substance are considered the same active substance, unless they differ significantly in properties in regards to safety and/or efficacy.	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 (MP) on the market, the reference should be the dosage form used for the initial approval of the concerned MP and which was used in the clinical efficacy and safety studies (if available).
USA	The formulation must be pharmaceutically equivalent to that of the reference listed drug (RLD).	An RLD means the listed drug identified by the FDA as the drug product upon which an applicant relies in seeking approval of its ANDA.
Russia	Pharmaceutically equivalent product (the same quantity of the same active substance in the same pharmaceutical form) or pharmaceutically alternative product (the same active substance in different chemical forms or in different pharmaceutical forms).	Original MP, if registered in the Russion Federation (RF), or its equivalent, if its bioequivalence to the original medicinal product has been established before and it has been successfully used in the healthcare establishments of the RF. The outcome of the BE study of the medicinal product registered in the manufacturing country can be considered acceptable, if the original medicinal product served as a reference product.

Test and reference products

Requirements still differ between countries / regions.

Region	Generic drug	Reference product
China	Essentially similar products, defined as either pharmaceutical equivalents or pharmaceutical alternatives.	The corresponding innovator's drug product *or* the major market corresponding drug product.

- Different salt, isomer, etc. can be used for the EMA but not for the FDA.
- China: BE to the innovator's product from the major market possible.
- Russia:
  - Possible to use another generic [*sic*] as reference which *'has been successfully used in the healthcare establishments of the RF'*. Example:
    $T_1 / R = 0.894$ (*CV* 20%, *n* 20, 90% CI 80.20–99.66% and is approved).
    Subsequently, T_1 is used as the 'reference' for another generic T_2.
    $T_2 / T_1 = 0.894$ (passes 'BE' and is approved).
    But: T_1 / R *would be* 0.894^2 or only 0.799 (90% CI 71.70–89.09%)!

Davit B, Braddy AC, Conner DP, Yu LX. *International Guidelines for Bioequivalence of Systemically Available Orally Administered Generic Drug Products: A Survey of Similarities and Differences*. AAPS J. 2013; 15(4): 974–90. DOI 10.1208/s12248-013-9499-x.

Test and reference products

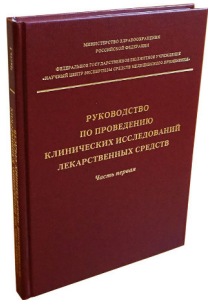
Requirements still differ between countries / regions.

- Russia:
  - The BE study with a foreign reference *'can be considered acceptable'*. However, the CRO has to be accredited* (forget studies outside the RF):
    - Federal Law on Circulation of Medicines (No. 61-FZ, March 2010; amended No. 389-FZ, December 2015).
      - » Chapter 7. Article 38. 7.
        Clinical trials of medicinal products for medical use shall be carried out in medical institutions accredited by the authorized federal executive body in the manner prescribed by the Government of the Russian Federation.
      - » Chapter 7. Article 38. 8.
        The list of medical institutions entitled to conduct clinical trials of medicinal products for medical use and the register of issued approvals to conduct clinical trials of medicinal products shall duly be published and posted on its official website in the "Internet" by the authorized federal executive body.
    - * http://grls.rosminzdrav.ru/Ree_orgCl2.aspx
      Click найти to retrieve the list of accredited institutions (1,222 with October 2016).

Test and reference products

Requirements still differ between countries / regions.

- Russia:
  - Three different regulations are applicable.
    - The BE guidance (2008).
    - The "Red Book" (2013). ISBN 978-8125-1764-9
      - Chapter 7 looks like a translation of the EMA's GL – incl. bioanalytical method validation, Two-Stage Designs and reference-scaling for HVDP(s), biowaivers by f_2-similarity, … Nonparametric comparison of t_{max} is mandatory!
    - Regulations conducting BE studies in the framework of the Eurasion Economic Union (2015).
      - Looks like another (improved?) translation of the EMA's GL, 'spiced' with parts of the WHO's guidance.
  - Result:
    - Applicants 'pick out the best' and hope that the 'Scientific Centre of Expertise of Medicinal Products' of the Russian Ministry of Health will accept it.



Designs

Requirements still differ between countries / regions.

Topic	Similarities	Differences
Size of biobatch	Most specify a minimum test product batch size.	EMA, FDA, Russia, WHO: A minimum of 10% of the commercial batch size or 100,000 units, whichever is greater. China: A scaled-up batch or a full production batch.
Basic design	The standard is a 2×2×2 cross-over. Replicated cross-over designs may also be used. Parallel designs may be used for long half-life drugs.	None.
Subjects	Healthy normal subjects, unless – for reasons of safety – it becomes necessary to employ patients.	Japan: Subjects with low gastric acidity (achlorhydric subjects) should be employed in cases where the use of the drug is not limited to a specific population and the test and reference products show a significant difference in *in vitro* dissolution at around pH 6.8, or between pH 3.0–6.8 for basic drugs. Not applicable for enteric coated products.
Age	Adults.	EMA, FDA: At least 18 years. FDA: 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. WHO: 18–55 years. Russia: 18–45 years. China: Not specified.

Designs

Requirements still differ between countries / regions.

Topic	Similarities	Differences
Body weight	Most specify a body weight range.	EMA, Russia: BMI within 18.5 and 30 kg/m^2. FDA: Individuals representative of the general population. WHO: Within an acceptable range according to accepted life tables. China: Within the normal range according to accepted normal values for BMI; avoid high variances in subjects' body weights. Japan: Not specified.
Sex, ethnicity	Females in the bioequivalence studies should not be pregnant.	EMA, FDA, WHO, Russia: Subjects can belong to either sex. China: Healthy male subjects recommended. Study population should be determined based on the specific situation for each drug product.
Number	Minimum of 12 subjects (with few exceptions).	China: 18–24. Japan: A sufficient number to show BE.
Geno-/ pheno-typing	Generally not mentioned.	EMA, WHO, China, Russia: Should be considered for safety or pharmacokinetic reasons.
Dose strength	Generally with the highest strength, unless reasons of safety justify use of a lower strength.	EMA if nonlinear PK: Depends upon the type of nonlinearity / underlying causes. If nonlinearity is characterized by greater than proportional increase in AUC, on at least the highest strength. If the nonlinearity is less than proportional and results from saturable absorption, on the lowest strength. If the nonlinearity is less than proportional due to limited solubility of the API, on two strengths.

Designs

Requirements still differ between countries / regions.

Topic	Similarities	Differences
Dose strength	Generally with the highest strength, unless reasons of safety justify use of a lower strength.	FDA if nonlinear PK: Depends upon the type of nonlinearity. If the non-linearity is characterized by greater than proportional increase in AUC with increasing dose, on at least the highest therapeutic dose. If the non-linearity is less than proportional and results from saturable absorption, on the lowest strength. WHO: Generally the marketed strength with the greatest sensitivity to BE assessment should be administered as a single unit.
Analyte	Measuring and requiring the parent drug to meet BE limits unless the parent cannot be reliably measured; measuring and requiring the major metabolite(s) to meet BE limits when the parent cannot be reliably measured.	EMA, Russia: Using the metabolite as a surrogate for an active parent drug is expected to be accepted only in exceptional cases; applicant should present any available data supporting the view that the metabolite exposure reflects parent drug and metabolite formation is not saturated at therapeutic doses. FDA: Summary statistics only and use as supportive data when metabolites are formed primarily by presystemic metabolism and contribute meaningfully to safety and efficacy. WHO: BE testing on metabolites when the parent is a pro-drug or the metabolites are formed primarily by presystemic metabolism and contribute meaningfully to safety and efficacy. Japan: Major active metabolites may be measured instead of the unchanged active ingredient, if it is rational.

Designs, analysis

Requirements still differ between countries / regions.

Topic	Similarities	Differences
Add-on, GSD, TSD	Must be specified in the protocol.	EMA, FDA, Russia, WHO: Two-Stage Design acceptable, adjusted significance levels predefined in the protocol. HC: Group-Sequential and Two-Stage Design acceptable. Japan: Add-on Design acceptable.
PK-analysis	Non-compartmental (NCA)	None.
PK-metrics	SD: AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, t_{max}, $t_{½}$, λ_z. AUC_{0-72} instead of AUC_{0-t}. MD: $AUC_{0-\tau}$, $C_{max,ss}$, $t_{max,ss}$, $C_{min,ss}$ or $C_{\tau,ss}$.	EMA: SD AUC_{0-72} instead of AUC_{0-t} for all IR products. MD $C_{\tau,ss}$. FDA: SD AUC_{0-72} instead of AUC_{0-t} if long half drug and low variability. FDA, HC: MD $C_{min,ss}$. Russia (2008): Additonally C_{max}/AUC. MR additionally $t_{75\%}$ (plateau time).
Statis-tics	Log-transformation (except t_{max}). ANOVA or mixed-effects model on log-transformed PK-metrics.	EMA, Russia: Fixed-effects model. FDA, HC: Mixed-effects model.

BE-limits

Requirements still differ between countries / regions.

Topic	Similarities	Differences
BE-limits and assess-ment of BE	90% confidence interval (CI) of *GMR* SD: AUC_{0-t} and C_{max}, MD: $AUC_{0-\tau}$ and $C_{max,ss}$ within 80.00–125.00%.	FDA: SD additionally for $AUC_{0-\infty}$. EMA: SD of MR additionally for $AUC_{0-\infty}$. Russia (2008): BE-limits 75.00–133.33% for C_{max}. WHO, Russia, China: Nonparametric test of t_{max} if clinically relevant. HC: BE-limits 80.0–125.0% for *AUC*s. *GMR* of C_{max} within 80.0–125.0% (*i.e.*, no CI is required). *GMR* of $C_{min,ss}$ >80.0%. China: BE-limits 70–143% for C_{max}. MD evaluation of fluctuation (%PTF) is a case-by-case determination. Japan: Products that do not meet BE-limits may still be deemed bioequivalent provided that the follwing three criteria are met: 1. The sample size is ≥20, 2. *GMR*s for *AUC* and C_{max} are within 0.9 to 1.11, 3. *in vitro* dissolution of the T and R is deemed to be the same under all conditions tested.

HVDP(s), NTIDs

Requirements still differ between countries / regions.

Topic	Similarities	Differences
HVD(P)s	Reference-scaling acceptable in some countries/regions. If acceptable, restriction of the *GMR* (within 80.00–125.00%).	EMA, Russia, WHO: Only C_{max} (EMA: additional PK-metrics for MR-products), CV_{wR} >30% demonstrated in a replicate design, upper cap of scaling 50%, method ABEL. High variability not caused by outliers. FDA: C_{max} and *AUC*, CV_{wR} ≥30% demonstrated in a replicate design, method RSABE. HC: Only *AUC*, CV_{wR} >30% demonstrated in a replicate design, upper cap of scaling 57.4%, method ABEL (but mixed-effects model). Japan: Approaches to reduce variability recommended, *i.e.*, a steady-state study or a study with a stable isotope simultaneously administered IV (to correct for variability in inter-occasion clearance).
NTIDs	More stringent acceptance intervals (AIs). Some countires/regions provide lists of drugs to which the more stringent AIs should apply.	EMA: In specific cases the AI for *AUC* should be tightened to 90.00–111.11%. Where C_{max} is of particular importance for safety, efficacy, or drug level monitoring the 90.00–111.11% AI should be applied. Decision if an active substance is a NTID on a case-by-case basis. FDA: Reference-scaling based on CV_{wR} in a 4-period full replicate design recommended in product-specific guidance. HC: AI for *AUC* 90.0–112.0, AI for C_{max} 80.0–125.0. WHO, China: The AI may need to be tightened based on clinical justification. Japan: Provides a list of NTIDs where the AI for *AUC* and C_{max} should be tightened to 90.00–111.11%.

Biowaivers

Requirements still differ between countries / regions.

Topic	Similarities	Differences
Proportionality biowaivers	Permitted for strengths of a solid dosage form, provided that 3 conditions are met: 1. BE is demonstrated *in vivo* for at least one strength, 2. *in vitro* dissolution testing is acceptable, and 3. strengths are proportionally similar to the strength that underwent acceptable *in vitro* testing.	No apparent ones. Cardot JM, García Arieta A, Paixão P, Tasecsk I, Davit B. *Implementing the Additional Strength Biowaiver: Reconciling Similarities, Differences, and Shared Challenges in the EMA and US-FDA Recommended Approaches.* In preparation 2016.
BCS-based biowaivers	Countries/regions that consider granting BCS-based biowaivers will not consider granting these for buccal, orally disintegrating, or MR solid oral dosage forms and NTIDs. Generic drug IR formulations under consideration for BCS-based class I biowaivers should not contain any excipients that can impact drug absorption.	EMA, FDA, WHO, Russia, HC: Consider granting biowaivers for BCS Class I and – given certain conditions – BCS class III drugs. Note: For various *specific* requirements see the guidelines. Japan: Not acceptable. Davit BM, Kanfer I, Tsang CT, Cardot JM. *BCS Biowaivers: Similarities and Differences Among EMA, FDA, and WHO Requirements.* AAPS J. 2016; 18(3): 612–8. DOI 10.1208/s12248-016-9877-2.

Outlook

Still a long way to go.

- General
  - PK-metrics (will the FDA ever drop $AUC_{0-\infty}$?)
  - HVDP(s) and reference-scaling
    - Metrics (EMA: C_{max} only, FDA: C_{max} and *AUC*, HC: *AUC* only).
    - Statistical methods (FDA: RSABE; EMA, HC, ANVISA, WHO: ABEL).
- For IR products the requirements are already very similar. More to be done with
  - Nonlinear PK (EMA: highest *strength*, FDA: highest *dose*).
  - NTIDs (EMA, HC, WHO, Japan: fixed narrower limits; FDA: reference-scaling).
  - Biowaivers in Japan (ICH Concept Paper …).
- MR products less harmonized.
- Collection of current regulatory documents: http://bebac.at/Guidelines.htm

Where are we going with Dissolution and BE Studies?

Thank You!

Open Questions?

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