EUROPEAN GENERIC AND BIOSIMILAR MEDICINES ASSOCIATION

Session 5 : Q&A on Other Important Topics

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Disclaimer

This presentation and session are aimed at facilitating a common interpretation of the guideline requirements and the presentation and session should not be interpreted as regulatory requirements. The contents of this presentation and session are subject to changes and should always be seen in conjunction with more recent official EMA and CMD(h) publications and decisions on the matter

1. Bracketing Approach (1/2)

Section 6.6. on Bracketing approach states :

"*In case bioequivalence assessment at more than two strengths is needed, e.g. because of deviation from proportional composition and/or if dissolution profiles are not similar, or for single unit formulations with proportional composition, a bracketing approach may be used if the other waiver criteria (see Guideline on the investigation of bioequivalence CPMP/EWP/QWP/1401/98) are fulfilled. In this situation it can be acceptable to conduct two bioequivalence studies, if the strengths selected represent the extremes, e.g. the highest and the lowest strength or the two strengths differing most in composition, dissolution or shape, so that any differences in composition or dissolution in the remaining strengths is covered by the two conducted studies.* "

1. Bracketing Approach (2/2)

- "if the strengths selected represent the extremes, e.g. the highest and lowest strength or the two strengths differing most in composition, dissolution or shape, it can be acceptable to conduct two bioequivalence studies only on the two extremes."
- **Please clarify what to do in a situation when these factors are not consistent with respect to the two extremes.**

2. Multiphasic MR products

- For multiphasic MR products, the different phases may not be apparent in individual subjects. Hence, the partial AUC and Cmax are likely to be highly variable with little clinical meaning. For the definition of time point for truncating, some multiphasic MR products have no specific justification because the reference SmPC has no documented clinical reason for having multiphasic release other than producing a loading dose from the IR portion.
- **Please clarify which approach should be followed in these cases.**

3. Variability of $C_{\tau,SS}$

- The variability of $C_{\tau,SS}$ can be very high for MR products with a short half-life and in some subjects, $C_{\tau,SS}$ may be under the limit of quantitation.
- **Please clarify how in this case data should be handled in the statistical analysis when log-transformation is applied?**

4. IVIVC

The guideline states (Appendix 3) : "An *in vitro in vivo correlation* (IVIVC) is a mathematical model describing the relationship between an *in vitro* property of a dosage form (mainly dissolution or drug release) and a relevant *in vivo* response (mainly drug plasma concentration or amount absorbed). It is self-evident that such a relationship is only likely to exist when the formulation controls the rate of appearance of drug in plasma.

- **When a modified release formulation is developed, it is highly recommended to establish an IVIVC?**
- **Please clarify what "highly recommended" means.**

5. Effects of Alcohol (1/4)

- **Paragraph 6.9 states : "***For generic oral formulations, in vitro studies of the release in alcohol solutions should be performed. Where accelerated active substance release is seen in vitro either at high or low alcohol concentrations over a short period of time or at lower alcohol concentrations over a longer period of time, the product should be reformulated.*
  If the alcohol effect cannot be avoided and it is present also in the reference product, the applicant should justify / demonstrate that it lacks clinical relevance or discuss the possible clinical relevance in comparison to the reference product."

5. Effects of Alcohol (2/4)

- **Please give examples of statistical tests that can be used for the comparison of the test and reference product in dissolutions with alcohol?**

5. Effects of Alcohol (3/4)

In case the alcohol effect is also present in the reference, a discussion on possible clinical relevance in comparison to the reference product is needed. The ultimate rationale for this is to establish measures for inclusion in the SmPC, which has already been done by the reference. All in all this exercise seems to be senseless for a generic, which must mimic the reference in all aspects. In fact, also the reference will need to be reformulated when an alcohol effect is present, so if the alcohol effect is still present it is to be assumed that reformulation was unsuccessful.

If, against expectations, the generic succeeds, how will the authorities handle this difference with respect to the reference?

5. Effects of Alcohol (4/4)

For generic oral [modified release] formulations, in vitro studies of the release in alcohol solutions should be performed.

We would like to ask whether the requirement for in vitro studies of the release in alcohol solutions also applies for multiple unit gastro-resistant formulations, e.g. beads/pellets in capsules.

- There is a common understanding that such small particles pass through the pylorus like liquids, hence there is no risk of prolonged residence in the stomach. Once the beads/pellets reach the small intestine, the release of drug substance is like an immediate release product.

Questions from attendants

6. Effects of saunas and sun creams

We would like further clarification on study designs exploring the effect of saunas and sun creams. What recommendations will be offered to companies seeking scientific advice on this topic, in particular are there any standards that could be recommended for either of these conditions?