EUROPEAN GENERIC AND BIOSIMILAR MEDICINES ASSOCIATION

Session 2 :Injectable Modified Release Products

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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. Waiving Single Dose Studies

The guideline says : ***"In case therapeutic doses cannot be administered to healthy volunteers, non-therapeutic doses may be acceptable for safety reasons. In situations where it is not possible to perform single dose studies with an intramuscular/subcutaneous depot formulation in healthy volunteers for safety or ethical reasons, multiple dose studies in patients are acceptable to show bioequivalence."***

Is the conclusion correct that a single dose study in patients is not required (if it is not possible to perform a single dose study with therapeutic doses or non-therapeutic doses in healthy volunteers) and that only a multiple dose study is required?

2. Criterion for waiving multiple dose studies (1/2)

- The criterion requires that the $AUC_{0-\tau}$ after the first dose covers more than 90% of the mean $AUC_{0-\infty}$ for both test and reference products.
- A criterion of 80%, which corresponds to an accumulation ratio of no more than 125%, is more consistent with the usual thinking that %ratio within 80-125% is not considered to be significant (e.g. criterion for non-linearity)
- **We would like clarification regarding the scientific rationale behind the 90%.**

2. Criterion for waiving multiple dose studies (2/2)

- **Does the requirement of a multiple dose study also apply to depot injectables intended to be administered once quarterly or even less frequently?**
- **In these cases a multiple dose study will necessitate an extremely long study which may not be practical. Moreover, the subject characteristics are likely to change during the long study duration, resulting in increased variability of the data.**
- **Considering that the single-dose data are more discriminatory in detecting formulation differences in PK, a waiver of the multiple dose study may be justified.**

3.Between-subject Variation (1/4)

- Many injectable MR products (e.g. depot formulation) tend to be long acting with a very long half-life. Hence, a parallel design is likely to be needed. The sample size of such parallel design studies could be very large as the between-subject variation is usually much higher than the within-subject variation. To avoid an extremely large sample size, there should be consideration of incorporating measures to minimize or eliminate factors that can significantly increase between-subject variability.
- The following example illustrates the impact of a variable elimination rate constant on the variability of AUC and Cmax

3.Between-subject Variation (2/4)

Adjust for human factors unrelated to formulation, e.g. elimination rate constant (kel)

Could adjust Cmax and AUC by kel

- Theoretically, AUC α 1/kel
- AUC*ke = (fraction absorbed)*(dose)/(volume of distribution)
- Eliminates effect of clearance

Cmax usually strongly correlated with AUC

3.Between-subject Variation (3/4)

Because PK analyses are done on ln-transformed data:

- ln(AUC * kel) = ln(AUC) + ln(kel)
- Perform analysis of covariance (ANCOVA) on ln(AUC) and ln(Cmax) with ln(kel) as covariate
- ANCOVA useful to remove influence of nuisance variables (e.g. kel) correlated with desired response variables [e.g. ln(Cmax), ln(AUC)]

e.g. Residual (within-subject) CV decreases from 68% to 22% for AUC and from 42% to 25% for Cmax after including ln(kel) as a covariate

3. Between-subject Variation (4/4)

Other subject-related covariates (age, weight, BMI, gender, etc.) could be included.

- If ANOVA of these covariates reveals no significant formulation effect (i.e. they are not formulation-dependent), is a covariance analysis including one or more of these covariates in the model acceptable in order to reduce the impact of between-subject variability on the comparison of the test and reference products?
- If yes, please suggest which factors may be included as covariates in the analysis of covariance? (For example, factors such as age, gender, body mass, terminal elimination rate constant)

4. Proportionality of injectable depot formulations

Chapter 6.4.2, page 23

"Only one strength has to be investigated if the different strengths are proportional in composition and exhibit a similar in vitro dissolution profile."

Multiple unit depot formulation could be proportional in composition for most excipients including the release-controlling ones, but not for the diluent (e.g. if the same volume is used in all strengths).

Please clarify what evidence (animal PK?) is expected to demonstrate that the non-proportionality in diluent volume has no impact on human PK - thus avoiding a second BE study (which in many cases is a multiple dose patient study, since the highest dose needs to be included).

Questions from attendants

5.Sites of administration

For IM depot injectables, where the SmPC specifies two sites of administration (e.g. gluteal and deltoid) would it be sufficient if only one site (e.g. gluteal) is used in the bioequivalence study for administration of both test and reference products?