EUROPEAN GENERIC AND BIOSIMILAR MEDICINES ASSOCIATION

Session 1 : Orally Administered Modified Release Products

Gerald Beuerle

Head of Clinical Development/Biopharmaceutics
European Scientific Operations, Teva / ratiopharm

Disclaimer

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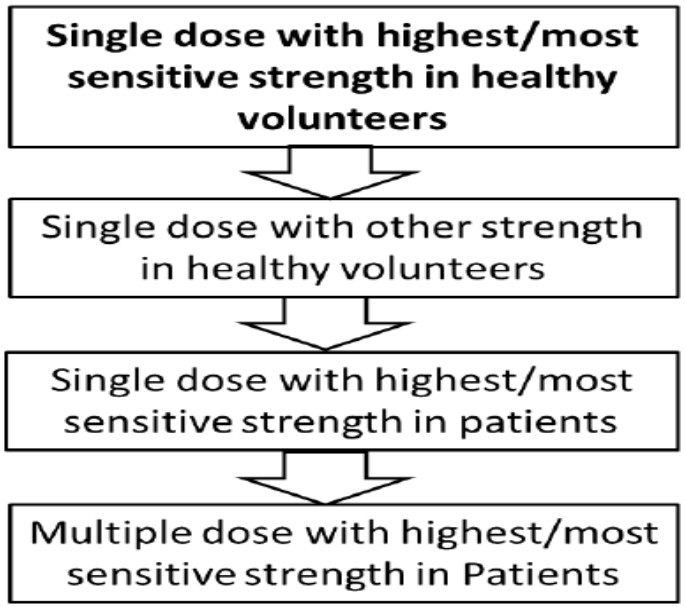
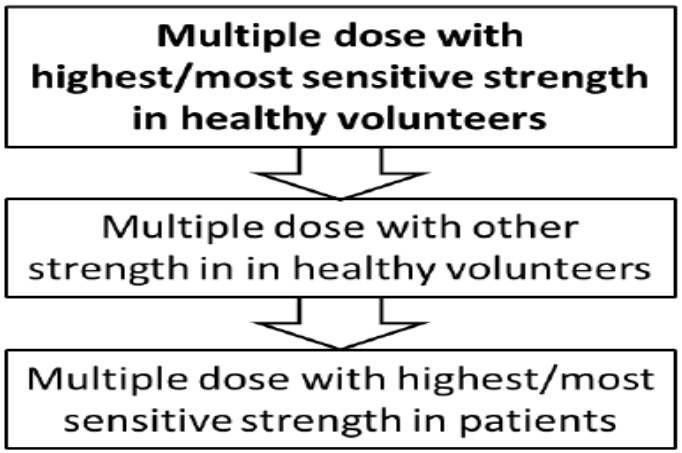
1. Multiple dose study in patients (1/2)

Chapter 6., page 17

"If it is not feasible to conduct single dose studies in patients, these can be replaced by multiple dose studies."





1. Multiple dose study in patients (2/2)

Where it is not feasible to perform single dose studies, these can be replaced by multiple dose studies in patients and a single dose study in the highest / most sensitive strength can be replaced by a multiple dose study in the highest / most sensitive strength.

We would like to confirm that this means that the multiple dose study in the highest strength which is required anyway is sufficient and no further studies are necessary (assuming criteria for extrapolation to other strengths are met)

2. Food-effect study (1/2)

Chapter 6.1.1.1., page 19

"Two cross-over trials. The first trial should compare the test and reference products under fasting conditions. The study treatments should be administered during two periods and with two sequences of treatment conditions. The second trial should compare the test and reference formulations following the administration of a high-fat meal at a specified time before taking the study treatment, as well as the test formulation under fasting conditions to generate intra-individual data describing a possible food effect."

2. Food-effect study (2/2)

One option is a 3-period crossover study with test and reference under one condition plus test under a different food condition

We would like to clarify if it is possible to add the administration under different food conditions as an additional arm in period 3 or if the study needs to be fully randomised.

3. Criterion for waiving multiple dose studies (1/4)

Chapter 6.1.1.2., page 19

"A multiple dose study is needed unless a single dose study has been performed with the highest strength which has demonstrated that the mean $AUC_{(0-\tau)}$ after the first dose covers more than 90% of mean $AUC_{(0-\infty)}$ for both test and reference, and consequently a low extent of accumulation is expected."

3. Criterion for waiving multiple dose studies (2/4)

Accumulation, i.e. $AUC_{0-\tau}$ steady state / $AUC_{0-\tau}$ after first administration is

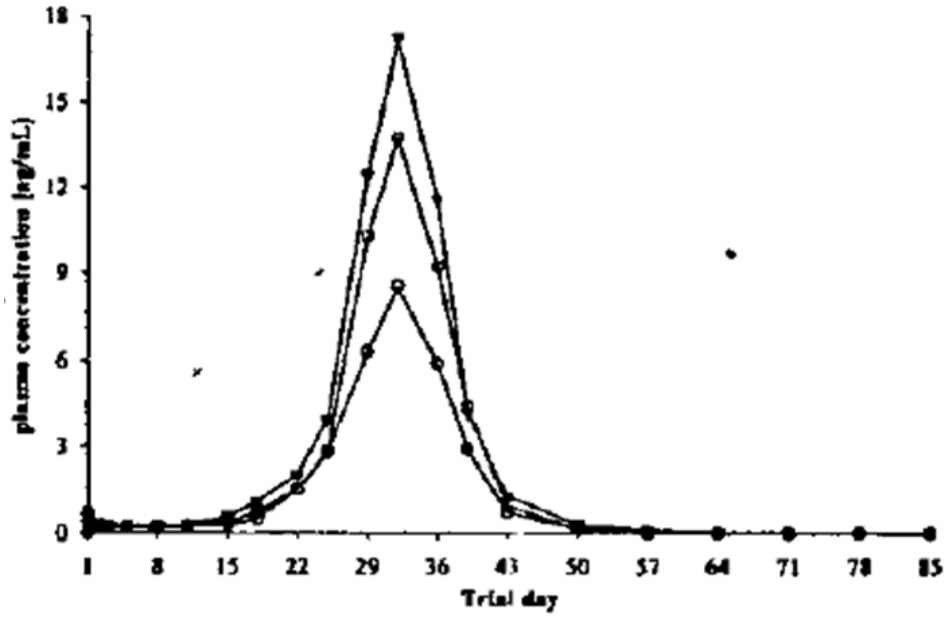
- 11% with the current 90% criterion
- 25% with an 80% criterion

For linearity assessment, a +/- 25% difference in AUC is acceptable.

We would like to get clarification regarding the rationale behind the 90% criterion.

3. Criterion for waiving multiple dose studies (3/4)

In products with a significant lag time, the current criterion for waiving the steady state study cannot be met although no accumulation occurs.



3. Criterion for waiving multiple dose studies (4/4)

We would like to clarify if in such cases the criterion could be modified to "... that the mean $AUC_{(x - (x+\tau))}$ after the first dose covers more than 90% of mean $AUC_{(0-\infty)}$ for both test and reference".

4. Cut-off time point for partial AUC (1/2)

Chapter 6.1.1.2., page 19

"An early $_{partial}AUC_{(0 - cut\text{-}off\ t)}$ and a terminal $_{partial}AUC_{(cut\text{-}off\ t - tlast)}$, separated by a predefined cut-off time point, e.g. half of the dosage interval is recommended, unless otherwise scientifically justified."

4. Cut-off time point for partial AUC (2/2)

For some MR products, half of the dosage interval may have little clinical relevance, other cut-off points like reference tmax may be more suitable.

Could you clarify in which cases other cut-off points like half of the dosage interval are accepted? What kind of justification for the cut-off time is expected?

5. Multiple dose study under fed conditions (1/2)

Chapter 6.1.1.2., page 19

"If the SmPC states that the product has to be taken in fed conditions only the study should be performed in fed conditions (standard meal) including the day of profiling."

It is not clear how much standardisation is necessary for the standard meal which should be given on all days including the day of profiling

5. Multiple dose study under fed conditions (2/2)

- **Is it necessary / sufficient to define a target range for the standard meal in terms of calories and fat / protein / carbohydrate content?**
- **Is it sufficient that the same meals are given during T and R administration, but not every day?**
- **Is it acceptable not to exclude subjects if they do not eat their meals completely?**

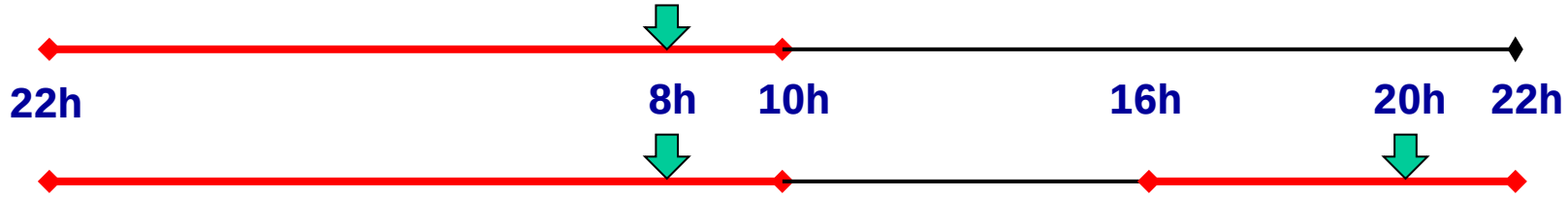
6. Multiple dose study, fasting conditions (1/2)

Chapter 6.1.1.2., page 19

"Fasting conditions in a multiple dose study need to be adapted to realistic situations, i.e. morning administration requires a 10 hour fasting interval whereas for all other administrations 4 hour fasting prior to administration is sufficient. Fasting after each administration should be defined as 2 hours minimum."

6. Multiple dose study, fasting conditions (2/2)

Strict requirements introduced, which may not be enforceable in some studies.



We would like clarification on the following points :

- **Is it possible to deviate from the requirements in case of patient studies or long titration periods or in case of more than once daily administration?**
- **We propose to use the strict requirements in such cases on the day of profiling (or a few days before)**

7.Assessment of steady state (1/2)

Chapter 6.1.1.2., page 19

"Whether the steady-state has been achieved is assessed by comparing at least three pre-dose concentrations for each formulation."

- **It is not clear whether steady state has already to be reached two administrations prior to profiling.**
- **Meeting the requirement can lead to very long study duration in case of long treatment periods.**

7.Assessment of steady state (2/2)

- It is not clear if c_τ can also be considered as “pre-dose value”.
- No recommendation for analysis of pre-dose values is provided

We would like to clarify the analysis to conclude on a steady state situation. Is a test for statistical differences of two pre-dose (prior to profiling) values acceptable, with an option to include c_τ, if necessary?

8.Shape of dosage form (1/2)

Chapter 6.1.2.1., page 20

"However, if the strengths of the test product do not fulfill these criteria or if the different strengths have different shape two strengths representing the most extreme difference should be tested in fed state."

It is not clear which shapes are considered different (e.g. round vs. triangular or oval vs. diamond). Additionally, selecting the extremes could be difficult. Definition of a parameter for shape and a similarity criterion would be helpful.

8.Shape of dosage form (2/2)

We would like clarification on the following points :

- **Which parameter could be used for defining shape and selecting the extremes, e.g. length to width ratio?**
- **When are shapes to be considered different (e.g. +/- 25% for the selected parameter could be similar)?**
- **What is the rationale for taking shape into consideration under fed conditions?**

9. Multiple dose study (1/2)

Chapter 6.1.2.1., page 20

"The other strength(s) can be waived if the criteria for waiver of strength described in section 4.1.6 of the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98) are fulfilled. However a bracketing approach (see section 6.6) is also possible if justified."

9. Multiple dose study (2/2)

In case that criteria for waiver of strengths are not fulfilled (deviation from proportional composition and/or dissolution profiles are not similar) more than one study needs to be performed.

Is there room for justification for a waiver of additional multiple dose studies with lower strengths, e.g. in case of formulations that are qualitatively identical and differ only slightly in quantitative composition and single-dose data demonstrate bioequivalence for lower strengths?

10. Criterion for excluding outliers (1/2)

Chapter 6.2.3., page 22

"… and can result in non-existing or aberrant concentration profiles. If the incidence of this outlier behaviour is observed with a comparable frequency (e.g. the number of cases is not numerically higher in the test product) in both, test and reference product, data of a period with non-existing or aberrant profile can be excluded from statistical analysis provided that it has been pre-specified in the study protocol."

10. Criterion for excluding outliers (2/2)

- "Numerically higher", if interpreted strictly, could mean a minor difference that does not reflect a pattern, but occurs by chance.
- Aberrant profile is not defined.

- **We would like to get clarification on the interpretation of "numerically higher".**
- **Do sponsors have to define a priori what is considered an "aberrant profile" in a specific study (e.g. less than 3 or 4 quantifiable concentrations)?**

11. Bracketing approach (1/2)

Chapter 6.6., page 24

"However, for prolonged release formulations release-controlling excipients and mechanism should be the same for all strengths of the test product. The same is required for release controlling coatings for delayed release formulations."

11. Bracketing approach (2/2)

There is uncertainty about the sameness criterion for release controlling agents.

We would like to clarify what "the same" means here:

- **Qualitatively the same?**
- **Quantitatively the same?**
- **With linear relationship between strengths?**
- **In same ratio if more than one release-controlling excipient is used?**

12. New strength (1/2)

Chapter 6.7., page 24

"For a new strength with non-proportional composition to approved strength(s), the new strength has to meet the requirements as described in relevant sections above (section 6.1-6.5)."

12. New strength (2/2)

If a biostudy needs to be performed, there may be situations where the reference dose cannot be administered through combination of available strengths.

We would like to clarify the expectations for the reference product in such situations. Should we try to come as close as possible and perform a dose-corrected evaluation (in case of linear PK)?

13. No truncated AUC (1/2)

Chapter 6.8.1.1., page 25

"A truncated $AUC_{(0\text{-}72h)}$ is not acceptable for MR products."

Since truncation of AUC at 72h is not acceptable, we would like to check alternatives for very long half-life drugs.

13. No truncated AUC (2/2)

We would like clarification on the following point :

Is it possible for long half-life drugs to deviate from the general requirement that 80% of $AUC_{(0-\infty)}$ is covered by $AUC_{(0-t)}$ if elimination is in the linear range, so a reliable estimation of $AUC_{(0-\infty)}$ is possible.

For orally administered products a truncation after 120h could be considered acceptable since no further absorption is to be expected.

14. Effects of alcohol (1/2)

Chapter 6.9., page 27

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

There is uncertainty which in vitro studies are to be performed.

14. Effects of alcohol (2/2)

We would like to clarify which in-vitro studies are necessary:

- **At 0 / 5 /10 / 20 % alcohol concentration?**
- **With QC medium?**
- **If QC method is complex (multiple media in staged approach) is it sufficient to cover the initial phase (e.g. 2 h in a gastric environment)**