Multibatch approach in BE testing

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EU regulatory requirement for choosing a representative batch

- Guideline on investigation of bioequivalence: one representative batch should be chosen for in vivo study based on in vitro tests
- PKWP QandA: for inhalational products FDC two batches may be used – one for each monocomponent

Inhalational products with high interbatch variability

- Symbicort (reference to budesonide/formoterol inhalational products) is known for its high interbatch variability
- Other example of OIP highly variable reference : Getz demonstrated bioinequivalence between Advair batches
- Is in vitro sufficiently predictive of in vivo performance?
- How to approach this problem?

Proposal for multibatch approach

- Paper by Sandell: *PK bioequivalence testing when between-batch variability is high: A multiple batch proposal*

- 10 000 simulations were performed based on 1,2, 4, 8 tests (AUC and Cmax with and without charcoal for each active)
- With increasing reference variability the probability to pass quickly decreases:

9 % difference=35% probability to pass 4 tests and 18% probability to pass 8 tests

- The idea of a multibatch approach: take several reference batches available on the market, mix them and compare to the test (either one batch or also several batches, depending on variability)
- 10 000 simulations with up to 10 reference batches

9 % difference=90% probability to pass 4 tests (no results for 8 tests)

Case study of hybrid formoterol budesonide OIP (reference: Symbicort Turbohaler)

PK study 1: An open-label, single-dose, randomized, five-period reference-replicate study to compare pharmacokinetic profiles of Test and Symbicort® Turbohaler®, with and without charcoal blockade, in healthy volunteers. One reference batch was used.

Reference variability was around 50 %

- PK study 2: an open-label, randomized, five-period, partially-replicated crossover, single-dose study to compare the pharmacokinetic profiles of Test and Symbicort Turbohaler with and without charcoal blockade, in healthy volunteers.
- 9 batches of reference were used (1 batch per sequence) and 1 batch of the Test
- Statistical analysis was standard
- Exposure was comparable between the test and the reference

The Scientific Advice

- Study results were presented at the SA with the question of acceptability of the multibatch approach
- If appropriately justified, the study design could be accepted; however the view of other member states is unpredictable
- PK data for each batch should be presented separately

Conclusion

- Multibatch in vivo approach could be a way forward for products with high interbatch variability
- Advantages:
- More realistic representation of the reference product
- Minimizes mismatch between in vitro and in vivo performance
- Other solutions also possible

- Regulatory acceptance of such design???

Thank you for your attention