Biowaiver of strengths for IR products

Industry perspective

BABE Workshop

Prague Sept 22nd, 2016

Presentation outline

Proportionality Criterion Considerations

Dissolution testing for biowaiver purposes

Bracketing

Biowaivers of Other Strengths

Proportionality Criteria

Biowaiver of Other Strengths
IR Products
General requirements EU

- *Biowaivers of other strengths*
  - *Same manufacturing process*
  - *Same qualitative composition*
  - *Proportional composition (except cosmetic coating)*
  - *In vitro similarity – in 3 media (normally pH 1.2, 4.5, 6.8) to the strength for which bioequivalence has been demonstrated in vivo*

Biowaivers of other strengths (IR) Proportionality criterion

- *(Directly) Proportional – IR Products*
  - *Ratio between the amount of each excipient to the amount of active substance(s) is the same*
    - *Coating components, capsule shell, colour agents and flavours are not required to follow this rule*
- *Acceptable deviations (still considered Proportional)*
  - *The amount of DS is < 5% of the tablet core/capsule content weight*

  and
  - *The amount of core excipients/capsule content are the same (only DS amount changed)*

  or
  - *The amount of the filler is changed to account for the change in amount of DS*

Biowaivers of other strengths (IR)
Wide strength range

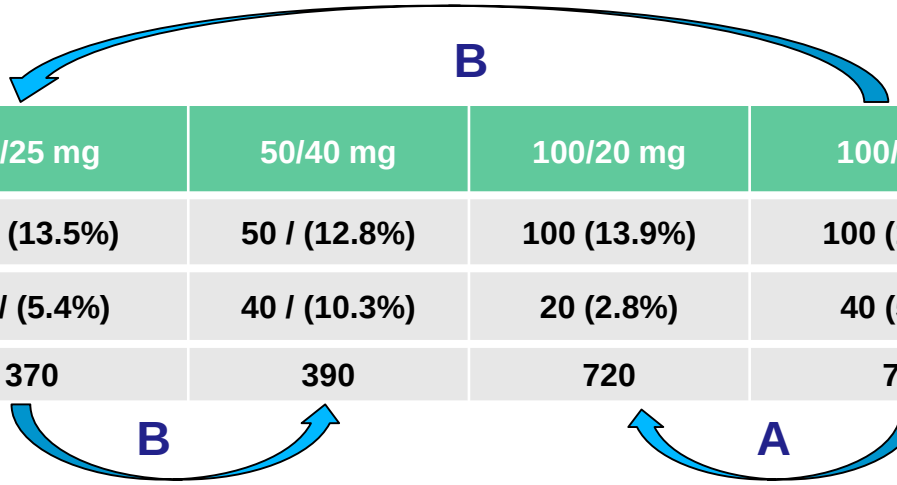
Drug substance (mg)	25	50	75	100	150	200	250	300
Total capsule fill weight (mg)	100	100	150	200	300	400	500	600
	Not proportional	Proportional						
	BCS biowaiver	Biowaiver to 300mg strength						BE study

- *For mono products*
  - *Similarity of size and shape or technological limitation may require 2 sets of proportional formulations to be developed*
  - *Bracketing, BCS-based biowaiver (if applicable) allow to limit the number of studies*

Biowaivers of other strengths (IR) Proportionality criterion

- *Fixed combinations*
  - *Proportionality criterion should be fulfilled for all active substances in fixed combination*
  - *When considering the amount of each active substance – other active substance(s) can be considered as excipients*
    - *For multi-layer tablets – each layer may be considered independently*
- *Bracketing*
  - *When deviation from biowaiver criteria exist – performance of 2 studies is acceptable if the strengths selected represent the extremes.*

Biowaivers of other strength
Fixed Combination – theoretical example



Strength	50/25 mg	50/40 mg	100/20 mg	100/40mg
Substance A [mg / (%)]	50 / (13.5%)	50 / (12.8%)	100 (13.9%)	100 (13.5%)
Substance B [mg / (%)]	20 / (5.4%)	40 / (10.3%)	20 (2.8%)	40 (5.4%)
Tablet core mass [mg]	370	390	720	740

- *(A) 100/40 to 100/20 waiver assuming small deviation for 5% rule is acceptable*
  - *„other active substance(s) can be considered as excipients" rule can be interpreted in more or less conservative manner*
- *(B) Waiver of 50/40mg study may be considered in special situation, based on other studies data indicating low risk of bio-inequivalence*

Bracketing

Biowaiver of Other Strengths
IR Products
Bracketing

- *Strengths selected must represent the extreme of deviation(s) from biowaiver conditions*
  - *Proportionality of strengths*
  - *Similarity of dissolution*
  - *Linearity of pharmacokinetics (under fasted and/or fed administration)*

$$A \approx B \text{ and } B \approx C \text{ and } C \approx D \text{ and } D \approx E$$

But

$$A \neq E$$

- *Identifying and assessing differences rather than similarities is required*

Biowaiver – Fixed Drug Combinations

- **For some DSs minor deviations like compensating the different amount of DS with a filler should not have impact on bioavailability based on published information, assuming in vitro similarity**

FOI: Study 302 (160/12.5 mg)	AUC (0-48) (h*ng/ml) Mean (SD)	Cmax (ng/ml) Mean (SD)
12.5 mg HCTZ in free combination	483.1 (87)	69.0 (14)
12.5 mg HCTZ in FDC	**481.6 (93)**	**69.2 (20)**

FOI: Study 303 (80/12.5mg)	AUC (0-48) (h*ng/ml) Mean (SD)	Cmax (ng/ml) Mean (SD)
12.5 mg HCTZ in free combination	466.5 (140)	72.1 (20)
12.5 mg HCTZ in FDC	**450.51 (118)**	**68.7 (21)**

- **Are such "pseudo-proportional type" deviations acceptable in justified cases?**

Source: 3rd EGA Symposium on Bioequivalence, June 2010

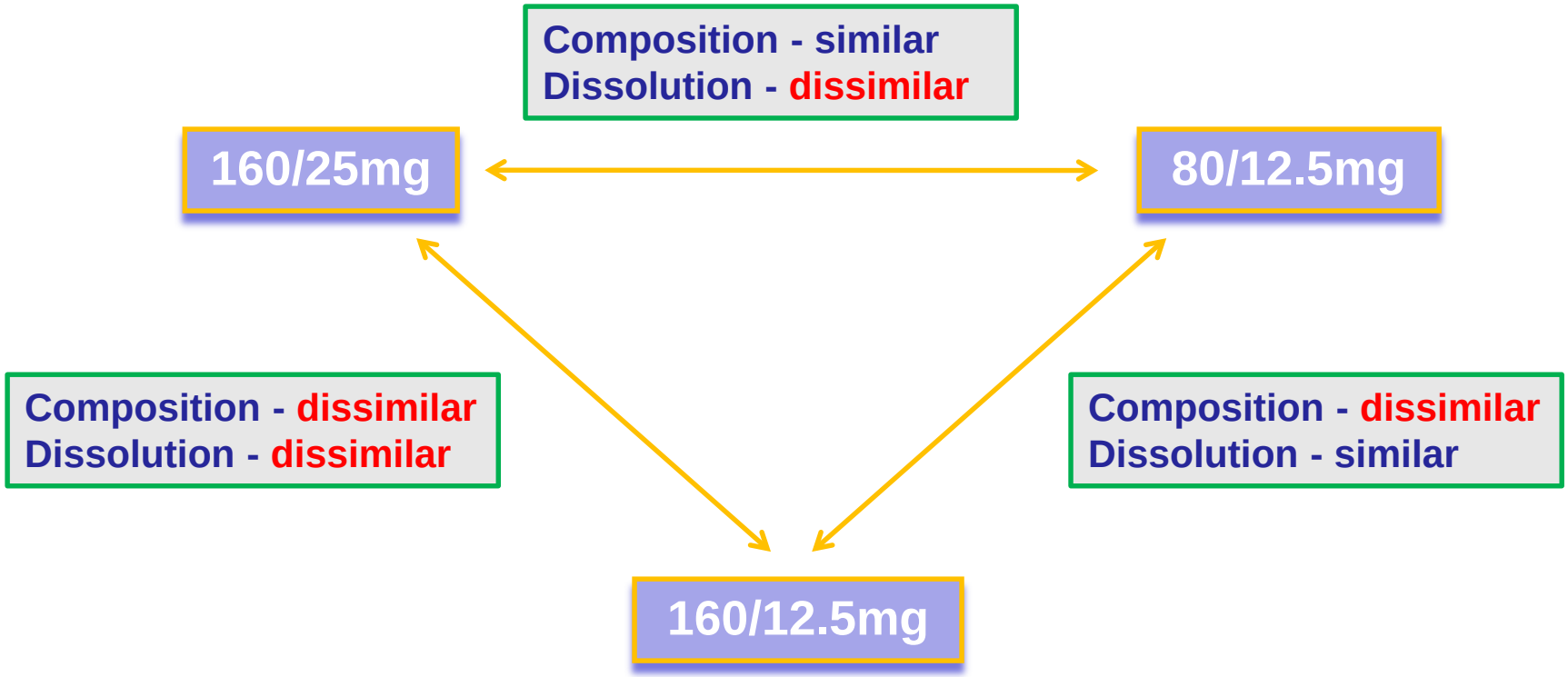
Biowaiver of other strengths – bracketing (1)

- For biowaiver of other strengths number of conditions need to be met
- Is bracketing considered suitable when products differ by more than one criteria (e.g. composition and dissolution)?

"Where bioequivalence assessment at more than two strengths is needed, e.g. because of deviation from proportional composition, a bracketing approach may be used. 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, so that any differences in composition in the remaining strengths is covered by the two conducted studies."

Source: 3rd EGA Symposium on Bioequivalence, June 2010

Biowaiver of other strengths – bracketing (2)



Demonstration of in vivo BE for 160/25mg and 160/12.5mg address both composition and dissolution differences (the two extremes), and allow for biowaiver for 80/12.5

Source: 3rd EGA Symposium on Bioequivalence, June 2010

Biowaiver of Other Strengths IR Products Bracketing

- *Identifying and assessing differences rather than similarities is required:*
  - *Qualitatively - areas that distinguishes the strengths*
  - *Qualitatively – magnitude of the difference present*
- *Open discussion on application of SUPAC-type criteria for deviation from proportionality is ongoing*
- *The rules for bracketing are not explicit, and in the presence of multiple differences (proportionality, dissolution) this approach may not be universally accepted in EU Member States*

Dissolution testing

Biowaiver of Other Strengths IR Products Dissolution testing

- *Similarity in 3 media (normally pH 1.2, 4.5, 6.8) of additional strengths to the strength for which bioequivalence has been demonstrated in vivo („within product series testing")*
- *At pH values where sink conditions are not achievable for all strengths in vitro dissolution may differ – testing should confirm that this is drug substance rather than formulation related*
  - *Comparison with the respective strength of the reference product - stated as required*
  - *Similar profile at the same dose within product series, e.g. 2x5mg vs 10mg - stated as optional*
- ***„The use of SLS in unacceptable in dissolution media for a waiver between strengths".***

Comments & Questions