CLINICAL ASPECTS OF THE DEVELOPMENT OF FIXED DOSE COMBINATION PRODUCTS

Jiří Haman

Marina Feřtek

State institute for drug control (SÚKL)

Abbreviations

- BE ≡ bioequivalence, bioequivalent
- BA ≡ bioavailability
- PK ≡ pharmacokinetic(s)
- CV ≡ coefficient of variation
- FDC ≡ fixed dose combination
- gFDC ≡ generic to FDC
- mono ≡ monocomponent of FDC

Content

- Background information of the bioequivalence drift
- Introduction to the new guideline for clinical devlopment of fixed dose combinations
- Specific aspects of the guideline

crossover design

- 3 treatments, 6 sequences, 3 periods
  - BE range (0.8, 1.25)
  - negligible period, sequence and subject effects
  - negligible value of inter- and intrasubject variability
- **BE based on comparison of point estimates**
- scenario with BE drift
  - mono is BE with FDC, FDC is BE with gFDC
  - mono **is not BE with** gFDC

simple scenario for BE drift (based on point estimates for mono, FDC and gFDC)

- **scenario 1: “mono < FDC < gFDC”**
  - let mono = FDC – C and gFDC = FDC + C
- **scenario 2: ”mono > FDC > gFDC”**
  - let mono = FDC + C and gFDC = mono – C
- let mono is BE with FDC and FDC is BE with gFDC
- we search for unknown constant C
- mono **is not BE** with gFDC if **C ≥ FDC/9**

Model situation of BE drift for Cmax (based on point estimates for mono, FDC and gFDC)

- mono = 88, FDC = 100, gFDC = 112
  - FDC – mono = 100 – 88 = 12,
  - gFDC – FDC = 112 – 100 = 12
- C = 12 > 100/9 = 11.11
  - mono/FDC = 88/100 = 0.88 (BE)
  - gFDC/FDC = 112/100 = 1.12 (BE)
  - … but gFDC/mono = 112/88 = **1.27 (not BE)**

BE drift – maximal relative difference (based on point estimates for mono, FDC and gFDC)

- **scenario 1: "mono < FDC < gFDC"**
  - mono/FDC > 0.8, gFDC/FDC < 1.25
  - then (gFDC/FDC)/(mono/FDC) < 1.25/0.8 = 1.5625
  - ***gFDC not bioequivalent with mono if BA of gFDC is at least 56.25% higher than BA of mono***
- **scenario 2: "mono > FDC > gFDC"**
  - mono/FDC > 0.8, gFDC/FDC < 1.25
  - … gFDC/mono > 0.8/1.25 = 0.64
  - ***gFDC not bioequivalent with mono if BA of gFDC is at least 36% lower than BA of mono***

Real-life situation

- Substitution indication: „this product is intended for patients already stabilized on monocomponents“
- Reference FDC authorized on bioequivalence with mono, gFDC on bioequivalence with reference FDC
- Prescription to the patient: stabilized on mono, prescribe gFDC
- Can we be sure that we reach the same plasma concentration, i.e. same efficacy and safety???

Current regulatory landscape

- Previous version of the FDC guideline issued in 2009
- In practice there was significant disagreement among member states on interpretation of Art. 10b
- To mitigate, CHMP issued a new draft in 2014
- Public consultations 2015
- New guideline valid from 1.10.2017

Main revisions

- Old version
  - Legal basis for FDC 10b
  - Combination packs acceptable in exceptional cases

- New version
  - Legal basis is Company´s choice
  - Guideline not applicable to combination packs, herbal FDCs, vitamins, oligoelements, minerals
  - Requirements for gFDC
  - Requirements for interaction studies for substitution indication

Documentation requirement – substitution indication

- PK: Bioequivalence study with mono
- Drug-drug interactions: literature or own study
- Efficacy/safety: literature (or study) demonstrating superiority of the FDC in comparison to the mono
- Coprescription data

Drug-drug interactions

- *Specific considerations apply for fixed combination medicinal products where the active substances have different – but related - therapeutic indications and different pharmacological targets…In addition, as a minimum requirement, in the absence of clinical trial, the potential for PK and PD interactions should be established to understand if the effect of the individual active substances may be modified by their combination. Usually, PK data (a DDI study) will suffice.*
- Not necessary to always perform a DDI study. If available, literature data is sufficient

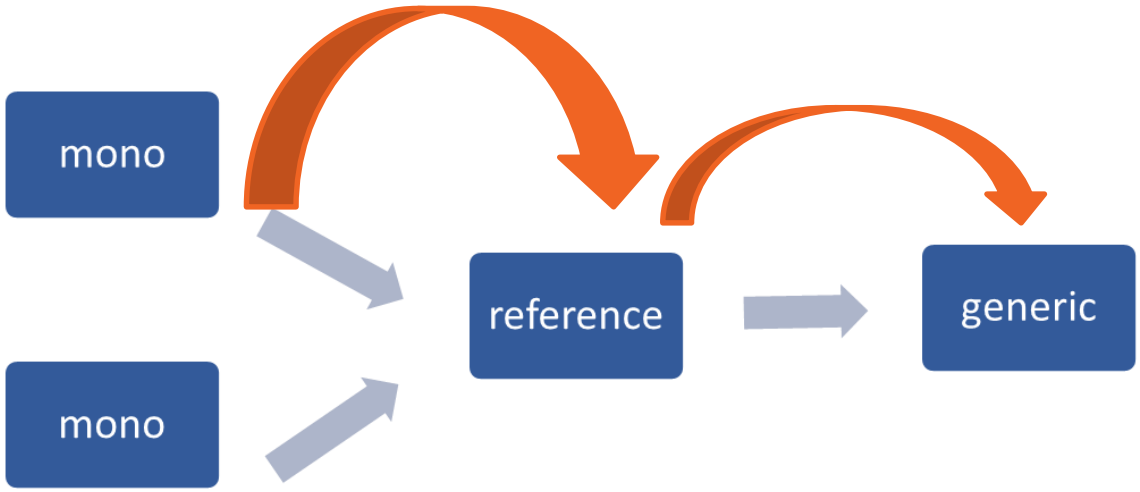
Drug-drug interactions

- CZ will continue to request interaction data
- Literature data is usually sufficient
- Literature should be substance-specific (no „class effect“ publications with consequent extrapolation to the specific substance)
- If no literature is available, the company should perform own DDI study

Generic fixed dose combinations

- Section 4.5 of the guideline: *Also, for generic fixed combination medicinal products it needs to be verified that the evidence base that may have been generated for the reference product with individual active substances (rather than with the fixed combination medicinal product, to which reference is being made) applies to the generic fixed combination medicinal product. In this case two pharmacokinetics bridges may need to be built, one between the reference fixed combination medicinal product and its active substances and one between the generic and reference fixed combination medicinal product. A justification should be provided why 'drifting' of bioavailability is not considered relevant and hence why the original demonstration of efficacy and safety is relevant to the generic.*

Generic fixed dose combinations



To conclude:

- Improvement of regulatory pathway of FDCs? Maybe…
- SUKL will validate FDCs under legal basis 8.3, 10a, 10b, 10.1
- Interactions should be part of the clinical package regardless of the type of actives
- In case of generics, pivotal data are gFDC to reference FDC

Thank you for your attention!

STÁTNÍ ÚSTAV PRO KONTROLU LÉČIV
Šrobárova 48, 100 41 Praha 10
tel.: +420 272 185 111
fax: +420 271 732 377
e-mail: posta@sukl.cz