Focus Group meeting on Bioequivalence

IFAH-Europe topics for discussion

EMEA, 6th May 2009

Content

1. Biowaivers, *E. De Ridder*
2. Statistical analysis, *U. Sent*
3. Study designs, *R. Hunter*
4. Others: API bioequivalence considerations and evaluating separate enantiomers, *M. Bobey*

1. Biowaivers: general

- **Golden rule** is **in-vivo bio-equivalence**!
  - PD or clinical endpoint only if in-vivo impossible
- Biowaiver principle is **acceptable and endorsed as such**
  - **If** equivalence is self-explaining and not-contested, e.g. IV aquous solution or inhalation gases
  - Discussion possible in other cases:
    - If criteria set for waivers for in-vivo test: **need for appropriate validation**
    - BCS or any other **system needs to be animal specific and validated**
    - Also **in feed in vivo is the golden standard** (premixes,...)

1. Biowaivers for *in vivo* BE ("6") for formulations

- **Identical** formulations OK
  - Identical API or comparable salt **might** be OK
  - ? Would this apply for all types of formulations?
- **IV** administration **only**
- Other p.e. administration of the same solution with same excipients
  - **No suspension, no emulsion**
  - What is **similar** amount of excipient?
- Oral solution if excipients do not impact GI transit, absorption, solubility nor in vivo stability of API
  - What is **similarity in excipients**?
  - New **formulation** should **only** contain **same API**?
- **Biowaiver according to BCS**
  - See below: appropriate validation!
- **Gases per inhalationem**

1. Biowaivers for *in vivo* BE ("6") for strengths

- In vivo waiver IF
  - Ànd in vitro equivalence data
  - Ànd all of the following conditions
    - Strengths manufactured "identical": same process, same manufacturer
    - Formulations identical qualitatively
    - Ratio API-Excipients the same
      - or if API <5% ratio between excipients similar (?)
    - Similar dissolution profiles under identical conditions
      - ? Appropriate conditions!
      - ? What is similar, we assume "7" applies?
        - » So 10%, or fully justified? How?
- Requires more clarity in wording

1. Biowaivers dissolution testing

- Design and use of *in vitro* tests to establish BE
  - The **apparatus** used for an *in vitro* BE study is **defined in the European Pharmacopeia**
  - The apparatus described is **specifically designed for human tablet formulations**
    - ***Not* capsules, boluses, or premix products**
    - **Tablet size may also be an issue with large animal products**
    - Buffer system – principal physiological buffer in all mammalian species GI tracts is not phosphate, but bicarbonate (the higher the concentration of bicarbonate, the faster the drug flux)
      - The inherent physiological complexity and variability of the GI tract across domestic veterinary species presents a truly complex system to attempt to mimic

Source: **Sheng et al., Toward an *In vivo* Dissolution Methodology: A Comparison of Phosphate and Bicarbonate Buffers. *Mol Pharm* 6: 29-39, 2009**

1. Biowaivers for *in vivo* BE ("5.3") for premixes and "drinks"

- **Assumption of waiver for oral solutions for drinking water**
  - Why no consideration of absorption here?
- Special consideration for **milk (replacer)** not defined…
- **In feed and in particular premixes**
  - Generally in vivo is possible now and should remain the golden rule
  - Waivers OK if appropriate
  - Current draft:
    - Only eligible if BCS I or BCS III
    - For BCS II and IV: seek scientific advice
  - QUESTIONS
    - Is BCS appropriately validated per species?
    - Assumption that excipients hardly have an impact in these formulations

1. Biowaivers

- **In vivo BE remains golden standard**
  - Analytical technology has progressed to allow measurement of an API (active) with low bioavailability Biowaivers should be granted when the appropriate criteria are fulfilled
- Complete waiver if proven **identical** products
- Any **dissolution tests must be species-specific and validated**
  - The **BCS system has not been scientifically validated or justified** to apply **to veterinary species**
- More **CLARITY** and **PRECISION** needed
  - Similar…
  - Seek advice…

2. Statistical analysis

Ref.:

- 5.15 Evaluation
- 5.15.1 Statistical analysis
- 5.15.2 Acceptance limits

5.15.1 Statistical Analysis

The current draft GL states

– For „all pharmacokinetic parameters under consideration“
  - Logarithmic transformation required
  - Parametric analysis mandatory (Variance analysis)

– We consider that this section needs further clarification and specification

5.15.1 Statistical Analysis

Standardisation of statistical analysis via log transformation and parametric analysis is considered justified for:

–Cmax and AUC (generally assuming normal distribution)

–But does not make sense for all PK parameters under consideration, like time dependent PK parameter (e.g. tmax)

Proposal

–Restriction to Cmax and AUC only, as the main PK parameter for BE

–Or maintain „all PK parameters“ and allow parametric and non-parametric analysis

5.15.2 Acceptance limits

The current draft GL requires

- Restriction of acceptance limits 80% to 125% for Cmax and AUC
- Increase in number of sample size in case of large individual variability
- We consider these requirements not justfied for Cmax, because
  - Cmax is a point value only
  - Narrow BE margin requires dense sampling around Cmax, which is not feasible in small species (cat, rabbit, etc...)
  - No acceptance limits defined for T_{max}

5.15.2 Acceptance limits

Cont‘d

– We consider these requirements not justfied for Cmax, because
  - Increase of sample size is not in agreement with 3R rules and would not add any value to the quality of data
  - Variability in Cmax will increase due to the fact that manipulations of dosage forms in order to obtain equal doses are not allowed

Proposal

- Maintain the acceptance limits of 70% to 143% for Cmax
- Depending upon study design, use of T_{max} to determine bioequivalence must be justified

3. Study Design

- Sections 1. and 2. appear to contradict each other:

    1. If PK endpoints cannot be used, then outside scope of GL

    2. Define if PK, PD, or clinical endpoints will be used

3. Study Design

5. “assumed that the applicant is familiar with pharmacokinetic principles”
   - This is a very dangerous assumption, as many, if not all, generic companies do not have this type of expertise on their payroll, nor do they always contract a consultant for it
   - This assumption leads to several approximations in the GL that may be problematic in the end

5.1 It is assumed that GLP applies to blood concentration studies and GCP to PD or clinical endpoint.

This needs to be clearly stated

3. Study Design

5.1 There appears to be a conflict of interest in requiring Scientific Advice to determine whether or not a crossover study can be used

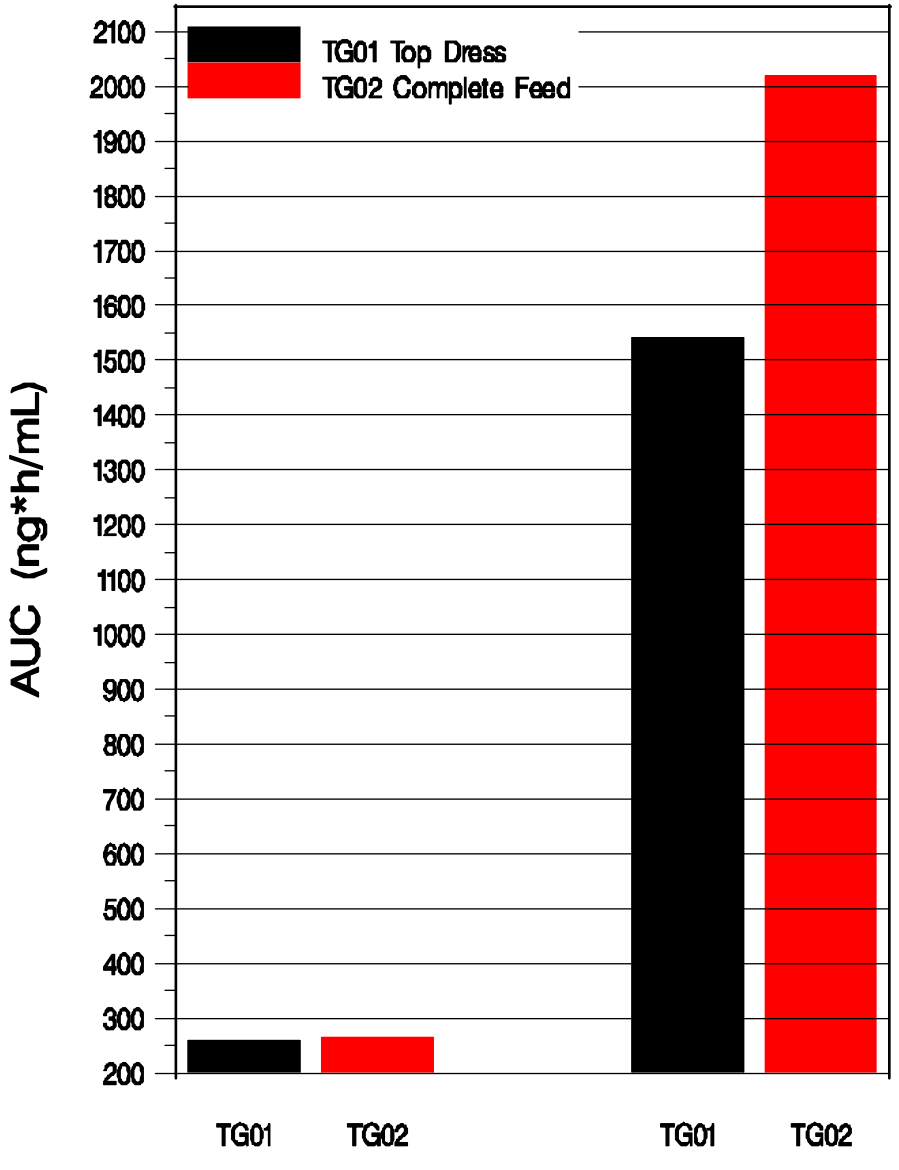
5.2 Definition of “modified-release formulation” is inaccurate and clearly derived from human use

3. Study Design: dose consideration

- Single dose studies are the norm (when required)
- Multiple dose studies needed as well
  - Single dose study indicated equivalence for two oral routes of administration for the same premix
  - Steady state data revealed different AUC at steady-state.
- Both single and multiple dose data should be required to establish bioequivalence with a sufficient level of certainty for products with multi-dose treatment regimens
- Use of overdose is allowed under specific circumstances
  - Demonstrated dose proportionality
  - Drug plasma levels difficult at use level
- Requirements on feeding status for monogastrics are unclear

3. Study Design: single dose vs. multi-dose studies

- Premix in cattle
- Topdress pellet vs. Complete feed (TMR mash)



4. Other items

- API bioequivalence considerations
- Evaluating separate enantiomers

4.1. Evaluating separate enantiomers

What reads in section 5.11 of the draft guideline:

- "Enantiomeric active substances" ⇨ unclear wording
- Section 5.11 limits the use of achiral bio-analytical methods to the following specific cases :
  - Both enantiomers have the same PK a/o the same PD a/o their concentration ratio is not modified in the rate of absorption
  - Both products contain the same single enantiomer and there is no in-vivo interconversion
- However, the purpose of the GL is "to define when Bioequivalence study can demonstrate that 2 products will show **similar safety and efficacy** in the target species" *(as per executive summary)*

4.1. Evaluating separate enantiomers

Our analysis:

- Art 13.2(b) of the Directive 2001/82/EC as amended: "The different (…) isomers, mixtures of isomers (…) shall be considered to be the same active substance, unless they differ significantly in properties with regard to **safety and/or efficacy"**
- Stereoisomerims is extensively reviewed in the GL on chiral subtances (EMEA/CVMP/128/95), and in particular:
  - Principles underlying choice of chiral/achiral methods are already described in section 6.6.
  - Safety and Efficacy of approved racemate (section 8) "is generally considered to be well established."

4.1. Evaluating separate enantiomers

Proposal:

⇨ Use a more commonly recognized wording ('chiral substance')

⇨ To avoid redundancies between texts and for clarity reasons, it is suggested to **refer to GL EMEA/CVMP/128/95** in replacement of lines 298-309 of the current draft.

4. 2. Complex study designs

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Further guidance needed in complex situations

- 3 way cross-over designs
- Studies in 'one-sample' animal species = sparse PK analysis
- Drugs that are active locally and systematically

But also re.:

- Wash-out periods
- Palatability considerations