REVISION OF CVMP GUIDELINE: CONDUCT OF BIOEQUIVALENCE STUDIES FOR VETERINARY MEDICINAL PRODUCTS

Main Changes to the Guideline

Fredrik Hulten, EWP
Karolina Törneke, CVMP
Piet-Hein Overhaus, QWP

Revision of Bioequivalence Guideline

Initial guideline came into effect July 2001

Draft Revised GL adopted at March CVMP meeting

Public consultation until 30 Sept 2009

Revision of Bioequivalence Guideline

Introduction and scope

New guideline rather than a revision…

- Clarifications and simplifications
- Generally similar or lower requirements
- Harmonisation with FDA
- Harmonisation with human side

To simplify life for all of us!

Introduction and scope

Strict definition of bioequivalence

- Both generics and product development
- BE (kinetic) only
- Palatability and compliance excluded
- Local effects excluded
- Comparative studies with pharmacodynamic and clinical endpoints excluded

It's about kinetics and the dose must be known and the exposure systemic!

Aspects related to the *in vivo* design

Dosing

- Special requirements in case of non-linear kinetics deleted
- Normally, any (approved) dose could be used with *in vitro* data to support other strengths
- Unit doses should not be manipulated
- The same amount should be administered in both periods

Aspects related to the *in vivo* design

Single versus multiple administration

- Single dose studies for all immediate release formulations
- Multiple dose studies only, in case of prolonged release formulations
- Food interaction should be considered in case of modified release formulations
- Requirements somewhat lower than human side

Aspects related to the *in vivo* design

Analytes

- Parent compound where feasible also in case of prodrugs
- Measurement of active metabolites normally not needed
- Achiral analytical methods accepted in case it is known that kinetics or dynamics is similar, or in case concentration ratio is not modified by a change of rate of absorption.

Aspects related to the *in vivo* design

Statistics

- Similar requirements as human side
- Detailed guidance
- Acceptance limits 0.80-1.25

Aspects related to the *in vivo* design

Exemptions

- Not much changed but the text is more clear and detailed
- Exemptions for im/sc injections in case of same excipients in similar amounts
- Introduction of BCS in veterinary medicine

Aspects related to the *in vivo* design

Complicated study designs?

- Several options with highly variable drugs (subjected to scientific advice)
- Parallel design studies acceptable if cross-over design is not feasible

We didn't find the "specific veterinary aspects" where we believe industry would like general advice (with one exception)

Aspects related to the *in vivo* design

Medicated feed with poorly soluble compounds

- The "Rate of absorption" is behaviour dependent
- Experimental designs (gavage, concentrate in "quick meal" etc) would measure something quite artificial and thus possibly overestimate differences
- A "field design" would be more clinically relevant but is likely to introduce too much variability

Could general guidance at all be given?

BCS System

BCS = Biopharmaceutics Classification System

Biowaiver = The possibility of waiving in-vivo bioequivalence studies in favour of specific comparative in-vitro testing in order to conclude bioequivalence of oral immediate release products with systemic action

- Highly soluble active substances, with known absorption in target animals and non-critical in terms of efficacy and safety

General considerations

Four Categories of Active substances

- ✓ **Class I**: high solubility, high permeability
- ✓ **Class II**: low solubility, high permeability
- ✓ **Class III**: high solubility, low permeability
- ✓ **Class IV**: low solubility, low permeability

- ➢ **Class I** and **Class III** might be eligible for a biowaiver

Summary Requirements

Biowaiver applicable for immediate release products if

❑ **Class I active substance**, and

- very rapid (more than 85% within 15 minutes) in-vitro dissolution characteristics of the test and reference product, and
- recipients which are not expected to have any relevant impact on bioavailability

❑ **Class III active substance**, and

- very rapid (more than 85% within 15 minutes) in-vitro dissolution of the test product and the reference product, and
- excipients are qualitatively the same and quantitatively very similar

Active substance

- Sound peer-reviewed **literature** may be acceptable for known compounds to describe the characteristics of the active substance
- Biowaiver may be applicable when the active substances in test and reference products are identical or belong both to the BCS-class I in case of **different salts**
- Biowaiver may not be applicable when the test product contains a different ester, ether, isomer, mixture of isomers, complex or derivative of an active substance than the reference product
- The active substance should not belong to the group of **'narrow therapeutic range'** medicinal products

Active substance - Solubility

- Highly soluble if the highest single amount is completely dissolved in a volume of buffer corresponding to the **gastric volume** of the target species
- Buffers within the range of possible physiological pH values (1 - 7.5) at 37°C - preferably at pH 1.2, 4.5 and 7.5
- Shake-flask method or equivalent

Active substance - Solubility

Species	Gastric volume
Cattle	200 litres (rumen)
Pre-ruminating calf	2 litres
Swine	8 litres
Horse	18 litres
Chicken	0.1 litres
Turkey	0.4 litres

Active substance - Absorption

- Complete absorption
  - Extent of absorption at least 85%
  - Related to high permeability

- Justification based on data from
  - Absolute bioavailability studies *or*
  - Mass-balance studies
    - recovery in urine and/or faeces of
    - parent compound and metabolites
  - In-vitro permeability investigations

Vet Med Product - In-vitro Dissolution

- General aspects
  - Test and reference product
    - similar in-vitro dissolution at pH 1.2, 4.5, and 7.5
    - surfactant strictly discouraged
    - test methodology preferably in accordance with pharmacopoeial requirements
- Evaluation
  - Test and reference product
    - ‘very rapidly’ dissolving if > 85% within 15 minutes
    - similarity of dissolution profiles may be accepted

Vet Med Product - Excipients

- Impact of excipients on the bioavailability of a BCS-class I active substance cannot completely excluded
- Biowaiver applied for a BCS-class III active substance, excipients have to be **qualitatively the same and quantitatively very similar** to exclude different effects on membrane transporters
- For both BCS-class I and III active substances in test like in the reference product **well-established excipients** in usual amounts should be employed and possible interactions affecting the active substance's bioavailability and/or solubility characteristics should be considered and discussed

Vet Med Product - Excipients

- So-called **'active' excipients** should be identified as well as their possible impact on
  - Gastrointestinal motility
  - Susceptibility of interactions with the drug substance
  - Drug permeability
  - Interaction with membrane transporters

Biowaiver for dosage forms for use in-feed

- May be treated as immediate release formulations and regarded as eligible for a biowaiver if they fulfil the BCS criteria
- Variability in feed constituents between test and reference product should not be greater than the natural variations that can occur in the final feed to which the animal will be exposed
- A product for use in-feed which contains insoluble constituents as excipients could also be eligible for a biowaiver, provided the active substance fulfils the BSC criteria

Biowaivers for soluble dosage forms for use in drinking water

❑ The conceptual basis for granting a biowaiver

- Presented in a solution prior to administration, the formulation will usually not influence the bioavailability of the active substance

- Rate-limiting step in systemic drug absorption will be
  a) the rate of gastric transit, and
  b) permeability of active substance across GI mucosal membranes

➢ Exceptions if excipients could cause a direct pharmacologic effect

Biowaivers for soluble dosage forms for use in milk/milk replacer

- Milk/milk replacer are not necessarily exactly the same as water, due to the potential for partition into the oil phase and/or binding to proteins
- For these products special consideration should be applied for granting a biowaiver