THE USE OF BIOWAIVERS IN DAILY PRACTICE

PROBLEMS, EXPERIENCE AND EXAMPLES FROM INDUSTRIAL PERSPECTIVE

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  - **Regulatory and scientific background**
  - **Practical problems from scientific background and sponsors input**
  - **Examples of identified objectives with various individual compounds**

BIOWAIVERS

- Regulatory background
  - Appendix III of the EMA guideline on the Investigation of bioequivalence CPMP/QWP/1401/98/Rev.1/Corr**. London 20 January 2010
- Scientific background
  - FIP Biowaiver Monographs, a list of approximately 45 publications of essential medical drug products published or in preparation

BIOWAIVER BACKGROUND

- Based on the BCS Classification system
- Applicable for BCS Class I products (high solubility and high permeability)

- Under certain conditions also for BCS Class III products (high solubility and low permeability)

- Applicable for immediate release products

BIOWAIVER BACKGROUND

- **High Solubility**
  - **If the highest single dose administered dissolves completely in 250 ml of buffer in the pH range of 1 – 6.8 at 37º C**

- **High permeability**
  - **If > 85 % of the drug administered is recovered as parent in urine and/or metabolites in urine based on absolute bioavailability data (nearly complete absorption) or mass-balance studies**

PRACTICAL PROBLEMS

- Since 2010 prepared over 30 biowaivers
- Most of them accepted by Regulatory Authorities
- Last 2 years regional difference observed in acceptance especially with newer drugs.
  - Some countries do not accept justications for biowaivers which are accepted by others (Examples) or ask for additional information.
- Practical problems finding the right justification for adequate permeability and solubility
- BCS classification (if published) may have conflicting information

SOLUBILITY

- Solubility data are not adequately available in public domain
- Sponsor did not sufficiently investigate solubility in accordance with biowaiver criteria
- Additional research required afterwards which is time consuming and causes delay in marketing authorization
- If not adequately justified biostudy will be requested

PERMEABILITY

- Permeability data not or insufficiently available in scientific literature
  - Absolute bioavailability data
  - Mass balance studies (Pharmaceutical companies tend to publish less as in the past)
- Next to literature public assessment reports can assist
- On www.drugs@fda.com biopharmaceutical and clinical pharmacology data are available from originator if drugs are registered in USA
- Other PAR's are usually less detailed

BCS classification

- Conflicting information in public domain
- Especially with product who are (nearly) insoluble in buffers at lower or higher pH media
- Additional solubility and dissolution studies required (Examples)

AMOXYCILLIN

- Company produced a series of Amoxicillin immediate release formulation among others tablets, capsules, dispersible tablets and powder for suspension in bottles
- For the powder for suspension the following strength were produced: 500, 400, 250, 125 and 100 mg/5 ml
- Bioequivalence was demonstrated with the highest and lowest strength against the European innovator as reference formulation
- Pharmaceutical similarity demonstrated for all formulations
- Dossiers accepted for marketing authorization in most European countries

AMOXYCILLIN

- Some Nordic countries have a different brand leader registered for these products which contain sugar, whereas the European brand leader and company's products are sugar free

AMOXYCILLIN

- The company produced a biowaiver based on the following arguments:
  - Amoxycillin is highly water soluble and has a high permeability (BCS Class I) with additional solubility tests in according to the guideline in all media
  - Amoxycillin is show linear PK behavior in oral doses up to 500 mg
  - Pharmaceutical similarity is demonstrated between the European brand leader, the Nordic products and their own product in accordance with the guideline
  - Amoxycillin absorption is not influenced by food (demonstrated in various studies with different formulations
  - Rate and extent of absorption is hardly influenced by type of IM formulation under fasting and fed conditions (various studies)
  - The amount of sugar is below 1500 mg/dose (highest dose) so effect on permeability is unlikely

AMOXYCILLIN

- All Nordic countries rejected the biowaivers and BE study (fasting only) was required against the Nordic brand leader
- Bioequivalence was proven in the study supporting the arguments of justification by the company

OSELTAMIVIR

- A company developed a generic version of Oseltamivir 75 mg tablets and conducted a biostudy versus reference formulation under fasted conditions in 2014 prior to the EMA product specific guideline was published.
- Based on scientific literature a Tmax between 0.9-1.8 hours was expected
- Based on available literature a sampling scheme was used with the following sample points:
- *“before study dosing (time “0”) and at: 15 min, 30 min, 45 min, 1 h, 1 h 15 min, 1 h 30 min, 2 h, 2 h 30 min, 3 h, 4 h, 5 h, 6 h, 8 h, 10 h, 12 h, 16 h, 24 hours after dosing”*.

OSELTAMIVIR

- Bioequivalence was concluded based on the following statistical evaluation

The 90% confidence intervals [3] of **oseltamivir** mean test/reference ratios were as follows:

Test name	Parameter	Test value (test/reference)	Lower 90% CI	Upper 90% CI	Bioequivalence assessment*
90% CI	$AUC_{0\text{-}t(last)}$	1.0190	0.9822	1.0571	YES
90% CI	C_{max}	1.0238	0.8733	1.2001	YES

** - If the values of CI lie within the predefined CI range (80-125 %) the equivalence can be concluded.*

OSELTAMIVIR

- The study was rejected by the Regulatory Authorities based on the fact that

- *It was observed that in about 32% of the study population Cmax was reached at the first time point of sampling for both test and reference treatments, which was totally unexpected based on the available scientific literature. Elimination of these subjects strongly reduced the power of the study results and thus would not conclude bioequivalence.*

OSELTAMIVIR

- Both test and reference products were pharmaceutical similar based on dissolution data in all media tested
- Maximum dissolution (nearly 100%) for both products was reached within 10 - 15 minutes in all media tested
- Company searched advise if a biowaiver was possible based on scientific literature and available data

OSELTAMIVIR EMA BE GUIDELINE

	☒ **fasting** ☐ **fed** ☐ **both** ☐ **either fasting or fed**
	Strength: 75 mg capsules because it is the highest strength **Background:** The highest strength is recommended for bioanalytical reasons. 75 mg is also the typical single dose for adults.
	Number of studies: One single dose study
	The solution may be waived if the same amount of sorbitol is used as in the originator.
Analyte	☒ **parent** ☐ **metabolite** ☐ **both**
	☒ **plasma** ☐ **blood** ☐ **urine**
	Enantioselective analytical method: ☐ **yes** ☒ **no**
Bioequivalence assessment	**Main pharmacokinetic variables:** AUC_{0-t}, Cmax
	90% confidence interval: 80.00– 125.00

* As drug variability has not been reviewed, this guidance is not applicable to highly variables drugs.

** The BCS classification should be confirmed by the Applicant at time of submission based on available data (solubility experiments, literature, etc.). If a drug substance has been classified as BCS class II or IV, no further solubility investigations are needed.

OSELTAMIVIR

- According to the available information a justications for a biowaiver was prepared with following arguments
- Oseltamivir is highly water soluble 586 mg/ml at 25ºC
- Oseltamivir has a high permeability with an absolute bioavailability over 85 % based on mass-balance studies with 14C-labeled material
- Both test and reference dissolve 100 % within 15 minutes in all media tested

OSELTAMIVIR

- The Regulatory Authorities issued additional questions
- Application of the in vivo study as an equivalent to bioequivalence study is conditional upon the following:
- 1. Documenting that oseltamivir belongs to specific BCS class (which is not unequivocally defined in the expert Report).
- 2. Total fulfilment of methodology and other aspects of the guidance specified in Appendix III to The European Medicines Agency, Guidance on the Investigation of Bioequivalence CPMP/QWP/1401/98 Rev. 1/Corr**.London. 20 January 2010.
- 3. Based on the reference literature and results of own research, presentation of analysis of correlation in vivo/in vitro.

CONCLUSIONS

- The use of biowaivers for the registration is very well possible for BCS class I and III immediate release formulation based on experiences in the past 7 years
- Last 2 years some countries are more strict in guideline interpretation than others
- Sponsors should be aware of providing all required information on solubility requirements in accordance with the BE guideline

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- **THANK YOU FOR YOUR ATTENTION**
- **DICUSSION**