Strength biowaivers and jurisdictional differences

Barbara M. Davit, Ph.D., Merck & Co.

Bioequivalence Workshop

Prague

September 21, 2016

MERCK
Be well

Disclaimer

I am an employee and shareholder of Merck & Co.

The comments presented are my own and not intended to represent those of Merck & Co.

Agenda

- Introduction
- Summary of regulatory guidance
- Case studies illustrating similarities, differences, and shared challenges

Introduction

Introduction

- In vivo bioequivalence (BE) studies compare the rate and extent of absorption of a test and reference drug product
  - New generics
  - Bridging formulations in new drug development
- Not necessary to conduct in vivo BE studies on all strengths of a drug product line
- Regulators permit waiving in vivo BE studies or “biowaivers” under some circumstances

Introduction

- This presentation will discuss similarities, differences, and shared challenges in biowaiver approaches between the US-FDA and EMA
- There are many similarities between the two jurisdictions
- There also exist differences which present challenges to firms seeking global registrations

Regulatory Guidance

Regulatory guidance governing biowaivers

- EMA, Guideline on the Investigation of Bioequivalence
- FDA, Draft Guidance, Bioequivalence Studies with PK Endpoints for Drugs Submitted Under an ANDA
- FDA, Draft Guidance, Bioavailability and Bioequivalence Studies Submitted in NDAs or INDs
- FDA, Guidance for Industry, SUPAC-IR

Case Studies

Case 1 – is a biowaiver feasible?

- Drug X is an IR formulation product line
  - 2.5, 5, 10 mg
  - In vivo studies against the 10-mg strength
- Can a biowaiver be applied in either of these cases?

Manufacturer	Total tablet wt	How varied
A	180mg	Filler (lactose)
B	205mg	Filler (lactose)

Depends on how proportional similarity is defined

- US-FDA – for high potency drugs
  - Total weight of dosage form nearly same for all strengths
  - Same inactive ingredients in each strength
  - Change in strength obtained by varying active and one or more inactive ingredients
- EMA uses the 5% rule
  - Amount of API must be < 5% of tablet core weight, and
  - Amounts of excipients are same per strength, or
  - Only the amount of a filler is changed to account for changes in API weight

Case 1: the outcome

- The US-FDA would grant the biowaiver in both cases
- The EMA would grant a biowaiver for mfr B, because all strengths meet the 5% rule
- The EMA would not grant a biowaiver for mfr A, because one of the strengths (10 mg) does not meet the 5% rule

Case 2 – is a biowaiver feasible?

API or excipient	5 mg	10 mg	20 mg	40 mg
API	5.00 mg	10.00 mg	20.00 mg	40.00 mg
filler	315.6 mg	148.3 mg	296.6 mg	291.1 mg
disintegrant	4.0 mg	8.0 mg	8.0 mg	8.0 mg
Core weight	410.0 mg	205.0 mg	410.0 mg	410.0 mg

- The 10-mg strength is ½ of the 20-mg strength in total weight
- Can biowaivers be granted for the 5- and 10-mg strengths?
- In the EMA, the 10-mg can be granted a biowaiver
  - Based on the 20-mg strength
- The EMA will not grant a biowaiver for the 5-mg strength
  - Against either 20- or 40-mg does not meet 5% rule
- Most likely, US-FDA may grant biowaivers
  - May combine approaches; sponsor should contact FDA

Fixed-dose combinations

- EMA
  - Conditions regarding proportional composition should be fulfilled for all active substances in the FDC
  - The other API is considered an “excipient”
- FDA
  - Bilayer tablets are considered one formulation even though they consist of different layers with different compositions
  - There should be proportional similarity within each layer

Case 3: biowaivers for FDCs

Ingredients	Tablet 1	Tablet 2	Tablet 3	Tablet 4
X (mg)	4	4	8	8
Y (mg)	5	10	5	10
Excipient 1 (mg)	80	80	160	160
Excipient 2 (mg)	80	160	80	160
Total wt (mg)	169	254	253	338

- EMA will consider bracketing
  - In vivo studies must be done at extremes
  - Extremes are 4/10 and 8/5
  - Although some jurisdictions may also request in vivo on 8/10 (highest) strength
- FDA will also consider bracketing
  - FDC considered one formulation
  - Extremes are 4/5 and 8/10; will request in vivo on these strengths

Case 4: biowaivers for bilayer FDCs

Ingredients	Tablet 1	Tablet 2	Tablet 3	Tablet 4
Layer 1 API X (mg)	4	4	8	8
Layer 1 excipient (mg)	80	80	160	160
Layer 2 API Y (mg)	5	10	5	10
Layer 2 excipient (mg)	80	160	80	160
Total (mg)	169	254	253	338

- EMA
  - The ratio of drug:excipient is constant within each layer
  - Will permit bracketing between 4/80 and 8/160
- FDA
  - All components of both layers should be proportionally similar
  - Will not permit biowaivers under strict interpretation of guidance

Case 5: an FDC with an IR and MR laye

- Drug X consists of a fast release layer and a prolonged-release layer
  - 10mg fast/30mg slow
  - 20mg fast/30mg slow
  - IR layer quantitatively proportional, PR layer is identical
- EMA will allow biowaiver for 10mg/30mg
- FDA will not allow biowaivers; entire formulation not proportionally similar
  - Concern about potential interaction between tablet layers

Case 6: biowaivers of new strengths of a generic drug product line

- A generic manufacturer markets 10-, 20-, 40-mg strengths of a product line, 10-mg strength scored
- What studies would be needed if desire to introduce a 5-mg strength?
- EMA – develop a 5-mg strength with a proportional composition or compatible with 5% rule
  - Biowaiver will be granted with acceptable dissolution
  - New strength not generic – hybrid application
- US – submit a Suitability Petition for new strength
  - Conduct an in vivo study, 2x5 versus 1x10
  - The new 5-mg strength becomes 5-mg reference

Conclusion

- There exists good convergence between US-FDA and EMA with respect to additional-strength biowaivers
- Significant differences still remain
  - In general, EMA guidelines provide specific recommendations
  - US-FDA guidelines provide more flexibility for showing proportional similarity (except for bilayer tablets)

Acknowledgements

- Jean-Michel Cardot, Ph.D.
- Alfredo García Arieta, Ph.D.
- Paulo Paixao, Ph.D.
- Ivana Taševská, Ph.D.