# An update on development strategies of recently approved biosimilars in Europe

**Johanna Mielke**

# Acknowledgement & disclaimer

*This project was supported by the Swiss State Secretariat for Education, Research and Innovation (SERI) under contract number 999754557. The project is part of the IDEAS European training network (http://www.ideas-itn.eu/) from the European Union's Horizon 2020 research and innovation programme under the Marie Sklodowska-Curie grant agreement No 633567.*

*The opinions expressed in this presentation and on the following slides are solely those of the authors and not necessarily those of Novartis, Sandoz, Bayer or the Swiss Government.*

Schweizerische Eidgenossenschaft
Confédération suisse
Confederazione Svizzera
Confederaziun svizra

IDEAS
Improving drug development

# Previously…

- Review of clinical development programs of 34 approved biosimilars on 12 different active substances
- Main source: European public assessment reports (EPAR)
  - Available online at http://www.ema.europa.eu
- Results:
  - Regulatory standards still evolving
    - High variability between submitted trials
    - Recently more non-standard approaches
  - Recommendation in product specific guidelines and overarching guidelines were mostly followed, but also exceptions
  - It is possible to gain approval even though not all pre-specified primary PK/PD endpoints meet the target

Mielke, J., Jilma, B., Jones, B. and Koenig, F. (2018): An update on the clinical evidence that supports biosimilar approvals in Europe. *British Journal of Clinical Pharmacology, 84 (7),* 1415-1431.
Mielke, J., Jilma, B., Koenig, F. and Jones, B. (2016): Clinical trials for authorized biosimilars in the European Union: a systematic review. *British Journal of Clinical Pharmacology*, 82 (6), 1444-457.

# Focus of today's talk

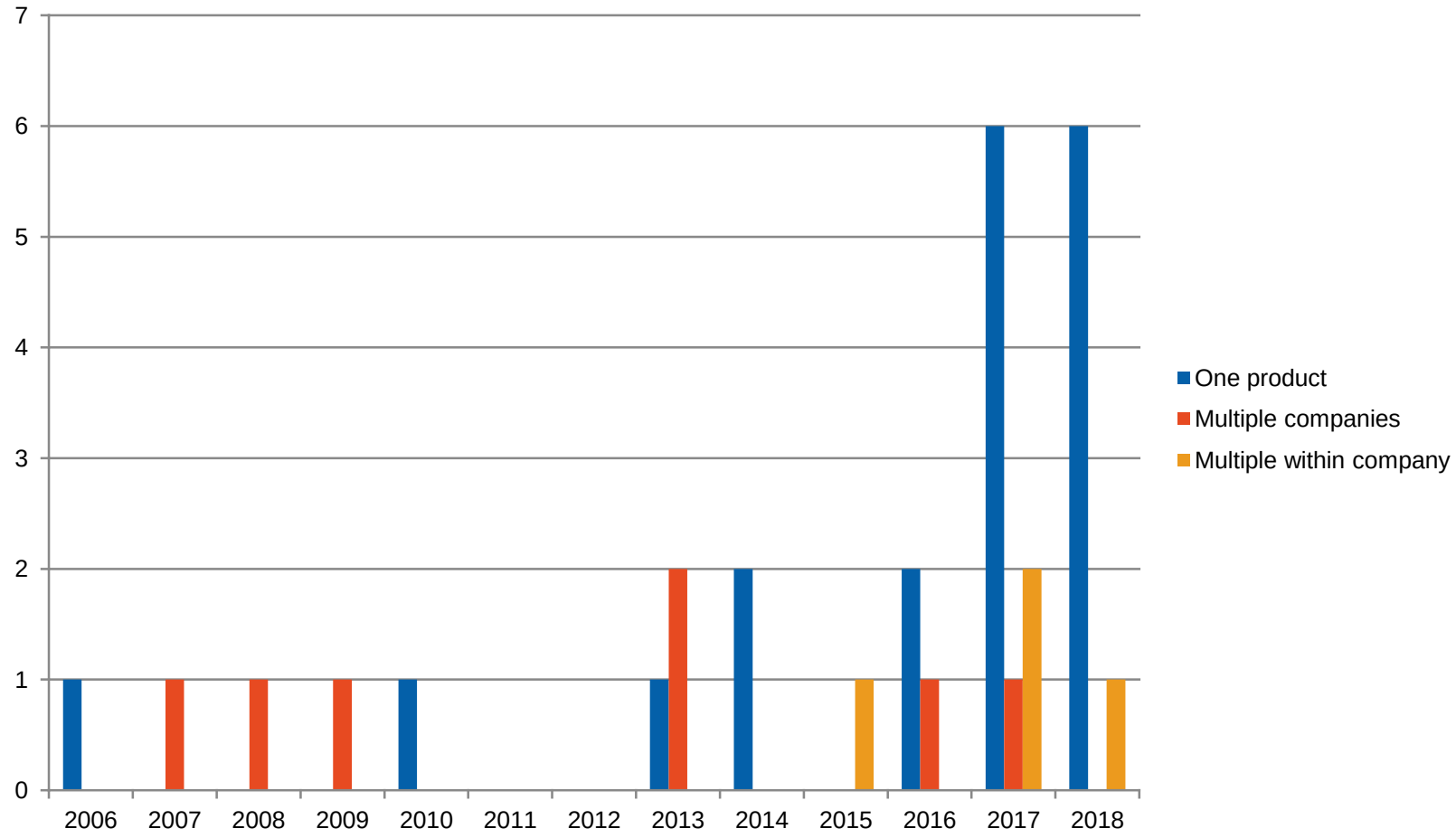
- Biosimilar landscape in Europe
- Global development programmes
- Heterogeneity of recently approved products

# Biosimilar landscape in Europe

# Products approved since last Biosimilar Forum

| Active substance | Originator drug name | Biosimilar |
|---|---|---|
| **Trastuzumab** | Herceptin | Ontruzant |
| | | Herzuma |
| | | Trazimera |
| | | Kanjinti |
| Infliximab | Remicade | Zessly |
| Adalimumab | Humira | Cyltezo |
| | | Halimatoz/Hefiya/Hyrimoz |
| | | Hulio |
| Insuline glargine | Lantus | Semglee |
| **Bevacizumab** | Avastin | Mvasi |
| **Pegfilgrastim** | Neulasta | Pelgraz (EC pending) |
| | | Udenyca (EC pending) |
| | | Fulphila (EC pending) |
| | | Pelmeg (EC pending) |
| | | Ziextenzo (EC pending) |

# Joint development programmes



# Multiple products – one company?

- Example: Amgevita/Solymbic (adalimumab)
- Approved indications

| Amgevita | Solymbic |
|---|---|
| Arthritis, Juvenile Rheumatoid | Hidradenitis Suppurativa |
| Arthritis, Psoriatic | Arthritis, Psoriatic |
| Arthritis, Rheumatoid | Arthritis, Rheumatoid |
| Colitis, Ulcerative | Colitis, Ulcerative |
| Crohn Disease | Crohn Disease |
| Psoriasis | Psoriasis |
| Spondylitis, Ankylosing | Spondylitis, Ankylosing |

# Global development programmes

# Motivation

- Companies often aim for approval in different regions, e.g., in the EU and in the US

| Active substance | Originator | Biosimilar EU | Biosimilar US |
|---|---|---|---|
| **Filgrastim** | Neupogen | Nivestim (2010) | Nyvestim (2018) |
| **Epoetin** | Epogen/Procrit | Retacrit (2007) | Retacrit (2018) |
| **Bevacizumab** | Avastin | Mvasi (2018) | Mvasi (2017) |
| **Adalimumab** | Humira | Cyltezo (2017) | Cyltezo (2017) |
| **Infliximab** | Remicade | Flixabi (2016) | Renflexis (2017) |
| **Adalimumab** | Humira | Amgevita (2017) | Amjevita (2016) |
| **Etanercept** | Enbrel | Erelzi (2017) | Erelzi (2016) |
| **Infliximab** | Remicade | Inflectra (2013) | Inflectra (2016) |
| **Fligrastim** | Neupogen | Zarzio (2009) | Zarxio (2015) |

- Options for development strategies
  - Conduct separate, independent development programmes for each of the regions
  - Global development programmes where parts of the assessments are used in multiple regions

# Regulations in Europe

*A single reference medicinal product, defined on the basis of its marketing authorisation in the EEA, should be used as the comparator throughout the comparability programme for quality, safety and efficacy studies during the development of a biosimilar in order to allow the generation of coherent data and conclusions.*

*However [...], it may be possible for an Applicant to compare the biosimilar in certain clinical studies and in vivo non-clinical studies (where needed) with a non-EEA authorised comparator [...].*

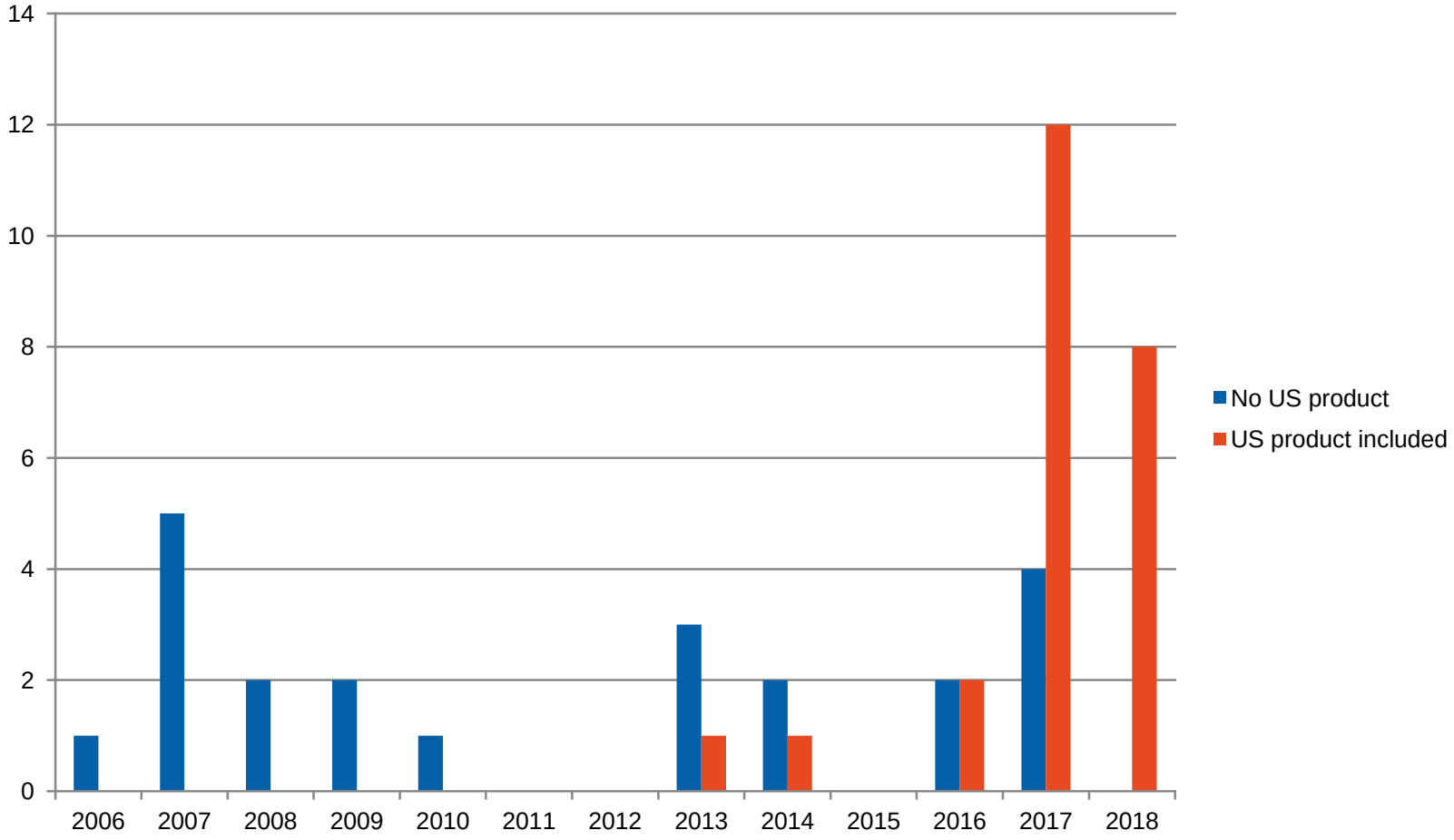
*As a scientific matter, the type of bridging data needed will typically include data from analytical studies (e.g., structural and functional data) that compare all three products (the proposed biosimilar, the EEA-authorised reference product and the non EEA-authorised comparator), and may also include clinical PK and/or PD bridging studies data for all three products.*

Guideline on similar biological medicinal products:
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/10/WC500176768.pdf

# Global development programmes in practice

- Aim: establish comparability of non-EU, EU, biosimilar
- In most cases:
  - Bridging study on analytical level
  - Bridging study on PK/PD level
  - Therapeutic equivalence and safety only with either EU **or** non-EU product
- Typical bridging study design on PK/PD level:
  - 3-way parallel groups design
  - 3-way crossover design
    (sequences: ABC, ACB, BAC, BCA, CAB, CBA)
  - (Two separate 2x2 crossover designs (non-EU vs. biosimilar; EU vs. biosimilar) and cross-study comparison)

# Trend to inclusion of the US product



# Example: Cyltezo (adalimumab)

| | Type of study | Study design | Sample size |
|---|---|---|---|
| 1 | PK | 3-arm parallel group (EU vs. US vs. biosimilar) | 193 |
| 2 | PK | 3-arm parallel group (EU vs. US vs. biosimilar) | 324 |
| 3 | Therapeutic equivalence | Parallel group (US vs. biosimilar) | 645 |

Bridging at PK level

Therapeutic equivalence & main safety study only with US product

*"Use of US-licensed Humira as the only comparator in this study is deemed acceptable due to a successful bridging exercise on the quality level, indicating similarity between EU and US reference, and successful bridging on PK level [...]."*

Gained approval in 2017 both in the EU and in the US.

EPAR Cyltezo: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/004319/WC500238609.pdf

# Example: Herzuma (trastuzumab)

| | Type of study | Study design | Sample size |
|---|---|---|---|
| 1 | PK | Parallel group (US vs. biosimilar) | 70 |
| 2 | PK | Parallel group (US vs. biosimilar) | 70 |
| 3 | Therapeutic equivalence | Parallel group (US vs. biosimilar) | 549 |

No clinical comparison to EU product!

*"The reference product, EU-Herceptin 150 mg/vial, has not been included in any clinical trial, therefore the bridge between the EU reference product and the comparator used in the clinical studies needs to be established based on physicochemical and biological similarity studies. The Applicant has addressed this as part of the 3-way similarity assessment for biosimilarity."*

Currently approved in Europe and under review in the US.

EPAR Herzuma: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002575/WC500249108.pdf

# Discussions

- Global development programmes for biosimilars seem to get more common in the recent years
- Bridging between EU and non-EU reference is mostly performed at PK level
  - First development program with bridging at analytical level only: Herzuma
- Global development programs seem to be well-accepted by regulators in Europe

# Heterogeneity of recently approved products

# Motivation

- We demonstrated earlier that the development programmes of biosimilars can differ in major points, even in case of an identical reference product
- Was this due to the lack of experience with biosimilars? Are more recent biosimilar development programmes more consistent?
- Case study: biosimilars with the reference product Herceptin (trastuzumab)
  - Ontruzant (Samsung Bioepis, approved 15.11.2017)
  - Herzuma (Celltrion, approved 09.02.2018)
  - Kanjinti (Amgen, approved 16.05.2018)
  - Trazimera (Pfizer, approved 26.07.2018)

# PK studies

| | Ontruzant | Herzuma | Kanjinti | Trazimera |
|---|---|---|---|---|
| Number of studies | 1 | 2 | 1 | 1 |
| Total number of subjects | 108 | 140 (70/70) | 157 | 105 |
| Study design of largest study | Parallel group | Parallel group | Parallel group | Parallel group |
| Dose | Single dose, IV, 6mg/kg | Single dose, IV, 6mg/kg | Single dose, IV, 6mg/kg | Single dose, IV, 6mg/kg |
| Study population | Healthy males | Healthy males | Healthy males | Healthy males |
| Primary PK endpoints | AUC(inf) | AUC(inf)<br>AUC(last)<br>Cmax | AUC(inf)<br>Cmax | AUC(inf)<br>AUC(last)<br>Cmax |

➔ Fairly consistent

# Therapeutic equivalence

| | Ontruzant | Herzuma | Kanjinti | Trazimera |
|---|---|---|---|---|
| Number of studies | 1 | 1 | 1 | 2 |
| Total number of subjects | 875 | 549 | 725 | 933 (707*) |
| Power | 80% | 80% | ? | 85%* |
| Study population | HER2-positive early breast cancer or locally advanced breast cancer | HER2-positive early breast cancer | HER2-positive early breast cancer | HER2-positive early breast cancer* |
| Primary endpoint | Difference in complete response rate | Difference in complete response rate | Difference in complete response rate | Risk ratio of overall response rate* |
| Equivalence margin | (-13,13) | (-15,15) | (-13, 13) | (0.8, 1.25)* |
| Result (95% CI) | (4.13, 17.26) Not equivalent | (-12.38, 5,16) Equivalent | (0.0, 14.6) Not equivalent | (0.842, 1.049) Equivalent* |

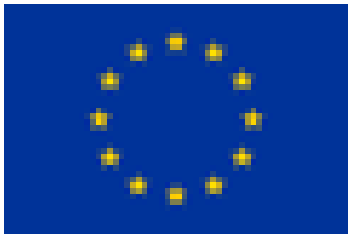
*: pivotal study

➔ Higher heterogeneity than for PK studies
➔ No standardisation of biosimilar development

# Conclusion

- Biosimilar landscape widened further in the last year
  - 17 new biosimilars approved
  - 3 new active substances
- Trend towards bridging studies
- Heterogeneity between biosimilar applications is still high
- First cases of gained approval with failed efficacy endpoint
- Some more complex statistical approaches, e.g., sequential testing strategy of efficacy endpoints for Kanjinti, but also many “standard” applications

Byron Jones
Franz Koenig
Bernd Jilma



# Thank you


This project was supported by the Swiss State Secretariat for Education, Research and Innovation (SERI) under contract number 999754557. The opinions expressed and arguments employed herein do not necessarily reflect the official views of the Swiss Government.

The project is part of the IDEAS European training network (http://www.ideas-itn.eu/) from the European Union's Horizon 2020 research and innovation programme under the Marie Sklodowska-Curie grant agreement No 633567.