BIOSIMILAIRES : UNE NOUVELLE FAÇON D'INNOVER?

Orateurs :
Bertrand POURROY – *La Timone, Marseille*
Françoise DE CROZALS – *Avignon*
Joseph CICCOLINI – *La Timone, Marseille*

Liens d'intérêts

- B. Pourroy

- F. De Crozals

- J. Ciccolini (2018-2019)

Institut Roche; Pierre Fabre; Ipsen; Novartis; Lilly; Astra Zeneca; BMS

Tout savoir sur les Biosimilaires

Bertrand POURROY
Pharmacien Clinicien
La Timone - Marseille

Françoise DE CROZALS
Pharmacien Clinicien
Avignon

Faut il avoir peur de la pharmacocinétique des biosimilaires?

Joseph CICCOLINI
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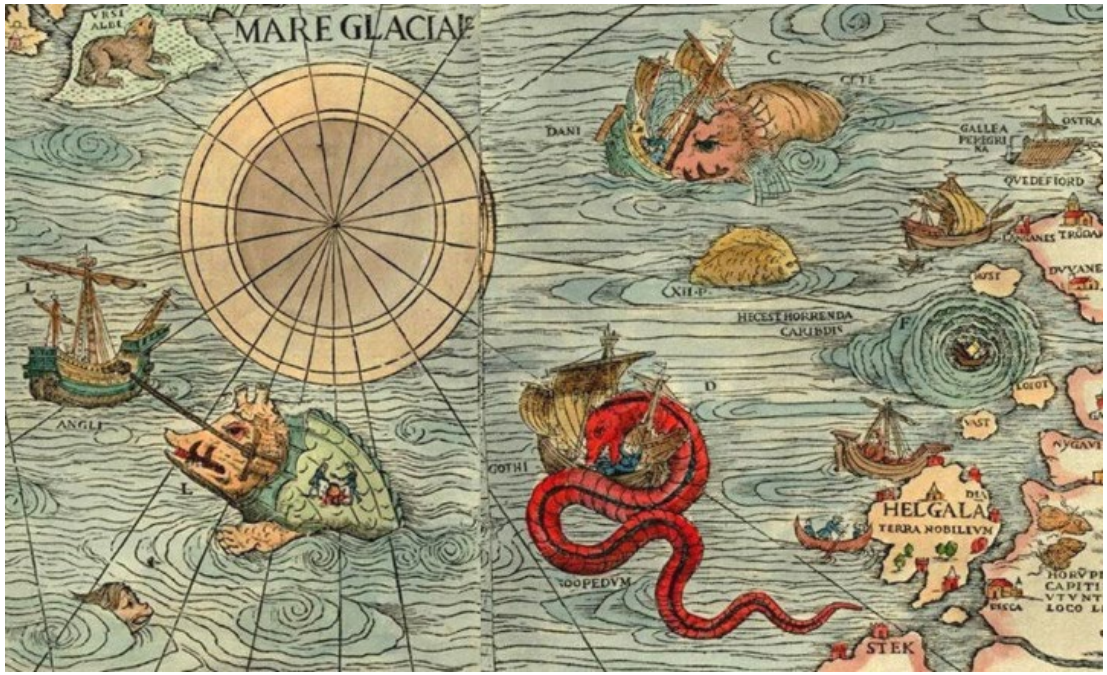
CHU Timone - Marseille
SMARTc CRCM Inserm U1068 - Marseille

Biologic's Pharmacokinetics

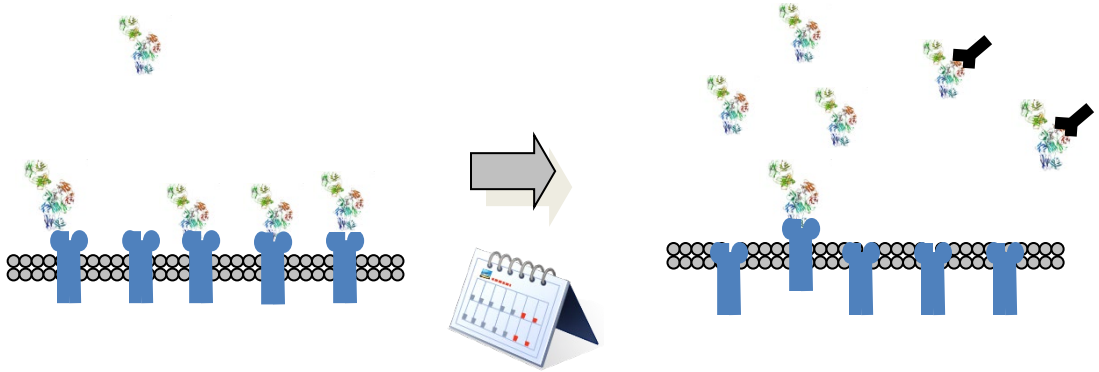


TERRA INCOGNITA

Biologic's Pharmacokinetics

- ✓ Hardly goes through membranes
- ✓ Long plasma half-lifes (i.e., weeks)
- ✓ No liver metabolism
- ✓ No renal clearance
- ✓ Low distribution phase
- ✓ Barely reaches tumor tissues
- ✓ Anti-Drug Antibodies

« receptor-mediated clearance » (RMC) a.k.a.
« target-mediated drug disposition » (TMDD).



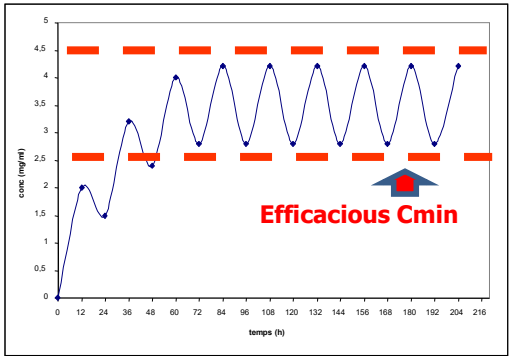
Dose-1
Day- 1

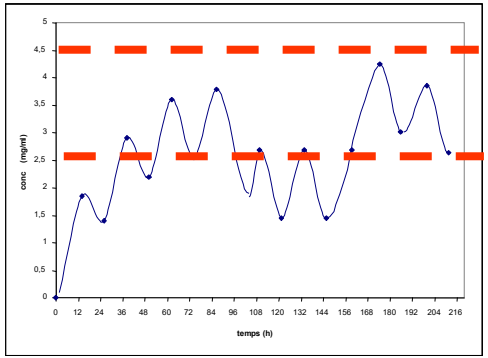
Dose-1
Day- n

Tumor burden+ receptor burden + anti-MoAB antibodies all impact on PK!

Non-stationnarity!

« receptor-mediated clearance » (RMC) a.k.a.
« target-mediated drug disposition » (TMDD).





C_{trough}: > 90% saturation
(depends on the target's Km)

Risk to miss the Therapeutic window!

Non-stationnarity!

WHO CARES ABOUT PK ?

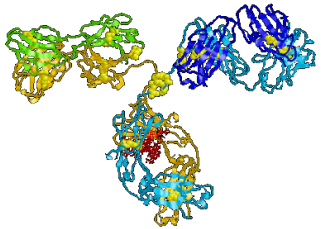
PK of biologics only starts to be considered!

Cytotoxics & TKIs

- Infusional or Oral absorption
- Goes through the membranes
- Strong liver metabolism
- Glomerular filtration
- Half-life in minutes / hours
- Extensive Distribution
- Biliary secretion

Biologics

- Little resorption through membranes
- Limited distribution
- No liver metabolism
- No renal clearance
- Half-life in weeks
- Proteolytic degradation
- Receptor-mediated clearance (TMDD)
- Anti-MAB antibodies



WHO CARES ABOUT PK ?

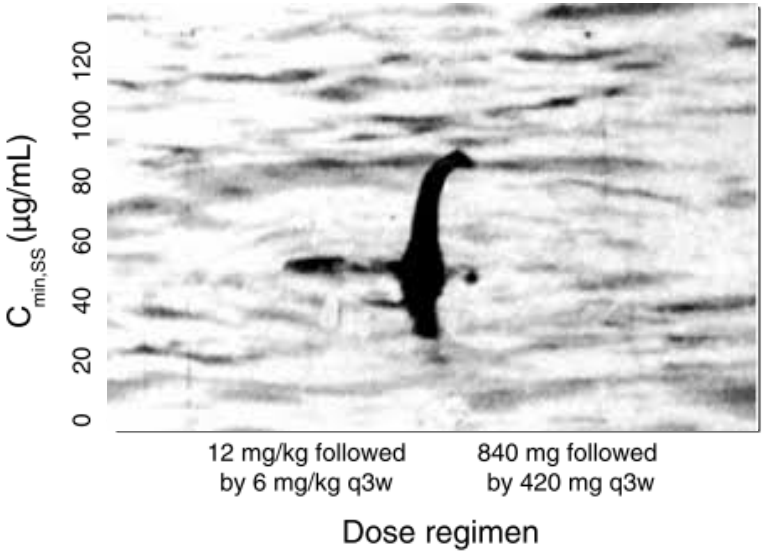
PK of biologics only starts to be considered!

- Impaired kidney function
- Impaired Liver function
- age
- obesity
- ADME genetic polymorphisms
- sex
- co-medications

- age?
- sex?
- tumor burden ?
- Fc-γ-R genetic polymorphism ?
- Albumin?
- ?
- ?

PK VARIABILITY WITH BIOTHERAPY IS NOT A HOAX!

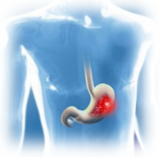
Pertuzumab (Perjeta®)



Garg A et al. Cancer Chemother Pharmacol 2014

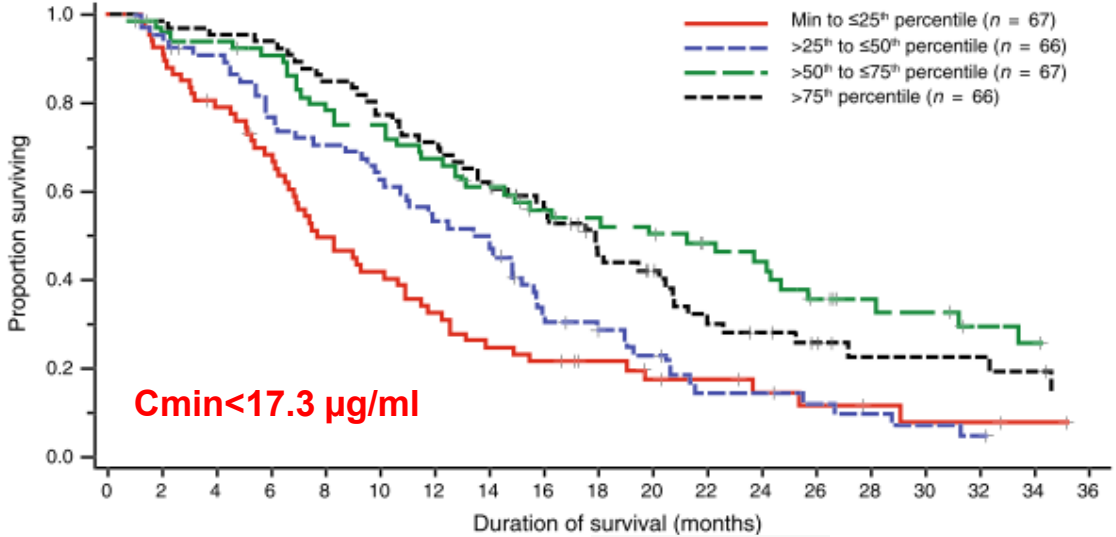
BIOTHERAPIES:
EXPOSURE MATTERS!

PK/PD OF BIOTHERAPIES



❖ **Trastuzumab in Gastric Cancer**

Cmin>36.9 µg/ml



Cosson et al. 2014

Trastuzumab (Herceptin®)

PK/PD OF BIOTHERAPIES

❖ **Bevacizumab in Colorectal cancer patients**

Clin Pharmacokinet (2016) 55:1381–1394
DOI 10.1007/s40262-016-0406-3

ORIGINAL RESEARCH ARTICLE

Bevacizumab Pharmacokinetics Influence Overall and Progression-Free Survival in Metastatic Colorectal Cancer Patients

Morgane Caulet[1,2] · Thierry Lecomte[1,2] · Olivier Bouché[3] · Jérôme Rollin[2,4] · Valérie Gouilleux-Gruart[2,5] · Nicolas Azzopardi[2] · Julie Léger[6] · Christophe Borg[7] · Jean-Yves Douillard[8] · Sylvain Manfredi[9] · Denis Smith[10] · Olivier Capitain[11] · Aurélie Ferru[12] · Driffa Moussata[2] · Eric Terrebone[13] · Gilles Paintaud[1,14] · David Ternant[1,14]

Published online: 16 June 2016

PK/PD OF BIOTHERAPIES

❖ **Cetuximab in Colorectal & Head and Neck cancers**

Ther Drug Monit. 2016 Jul 4. [Epub ahead of print]

Cetuximab pharmacokinetics influences overall survival in head and neck cancer patients.

Pointreau Y[1], Azzopardi N, Ternant D, Calais G, Paintaud G.

Cancer Therapy: Clinical

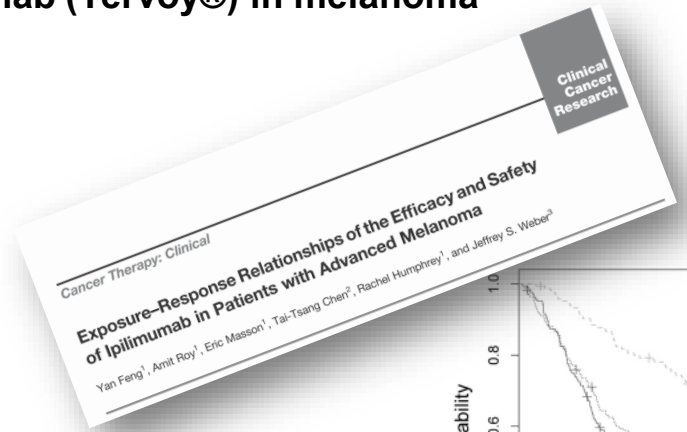
Clinical Cancer Research

Cetuximab Pharmacokinetics Influences Progression-Free Survival of Metastatic Colorectal Cancer Patients

Nicolas Azzopardi[1,2], Thierry Lecomte[1,2,3], David Ternant[1,2,4], Michelle Boisdron-Celle[6], Friedrich Piller[7], Alain Morel[6], Valérie Gouilleux-Gruart[1,2,5], Céline Vignault-Desvignes[1,2,4], Hervé Watier[1,2,5], Erick Gamelin[6], and Gilles Paintaud[1,2,4]

EXPOSURE LEVELS & PK VARIABILITY WITH IMMUNOTHERAPY PROBABLY MATTER!

❖ **Ipilimumab (Yervoy®) in melanoma**

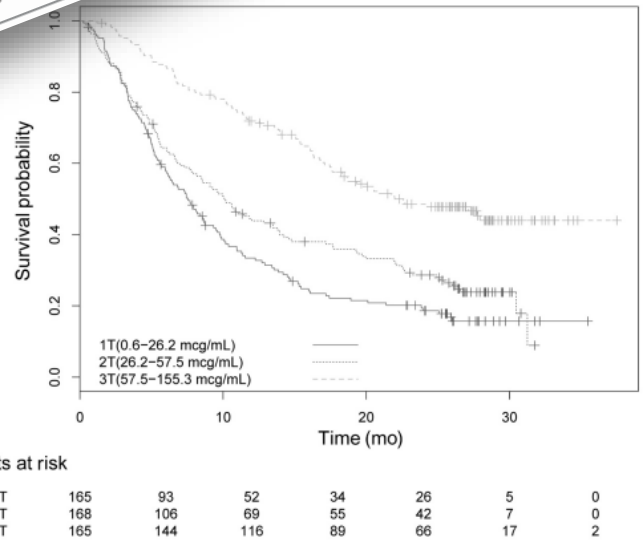

Cancer Therapy: Clinical

Clinical Cancer Research

Exposure–Response Relationships of the Efficacy and Safety of Ipilimumab in Patients with Advanced Melanoma

Yan Feng[1], Amit Roy[1], Eric Masson[1], Tai-Tsang Chen[2], Rachel Humphrey[1], and Jeffrey S. Weber[3]

Exposure Matters with IOD's!



Subjects at risk

1T	165	93	52	34	26	5	0
2T	168	106	69	55	42	7	0
3T	165	144	116	89	66	17	2

EXPOSURE LEVELS & PK VARIABILITY WITH IMMUNOTHERAPY PROBABLY MATTER!

❖ **Durvalumab (Imfizi®)**

ARTICLES

Population Pharmacokinetics of Durvalumab in Cancer Patients and Association With Longitudinal Biomarkers of Disease Status

Paul G. Baverel[1], Vincent F.S. Dubois[1], Chao Yu Jin[2], Yanan Zheng[2], Xuyang Song[3], Xiaoping Jin[3], Pralay Mukhopadhyay[4], Ashok Gupta[3], Phillip A. Dennis[4], Yong Ben[4], Paolo Vicini[1], Lorin Roskos[3] and Rajesh Narwal[3]

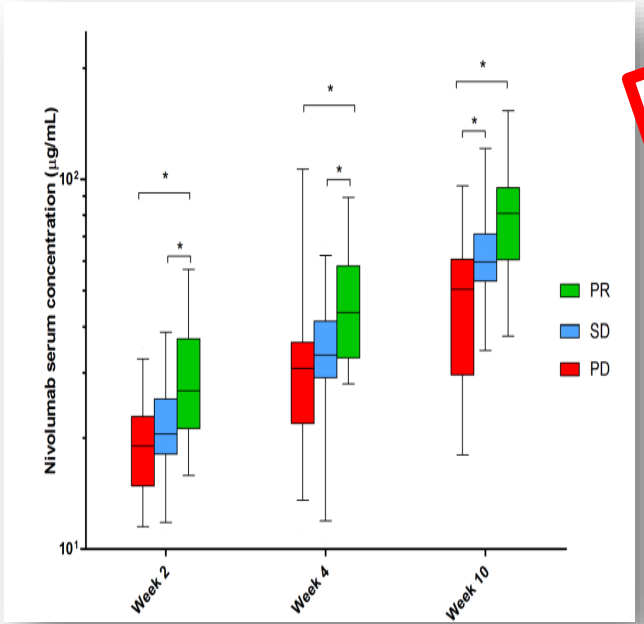
Exposure Matters with IOD's!

50µg/ml Ctrough level

Residual concentrations must be above a threshold to ensure target engagement!

EXPOSURE LEVELS & PK VARIABILITY WITH IMMUNOTHERAPY PROBABLY MATTER!

❖ **Nivolumab (Opdivo®) in lung cancer**



Exposure Matters with IOD's!

2018 ASCO® ANNUAL MEETING
DELIVERING DISCOVERIES: EXPANDING THE REACH OF PRECISION MEDICINE

EXPOSURE (TROUGH LEVELS) DOES MATTER!

Biosimilars & PK

✓ Patents are falling (ex: trastuzumab, rituximab, becacizumab…)

✓ It is possible to copy formely-patented drugs!

✓ New players in the game!

Biosimilars & PK

Company	Biosimilar	Submitted to EMA	Submitted to FDA
Amgen	ABP 980	March 2017	July 2017
Biocon/Mylan	MYL-1401O	August 2016	November 2016
Celltrion	CT-P6	October 2016	July 2017
Samsung Bioepis	SB3	August 2016*	
Pfizer	PF-05280014	July 2017	Submitted (date unknown)

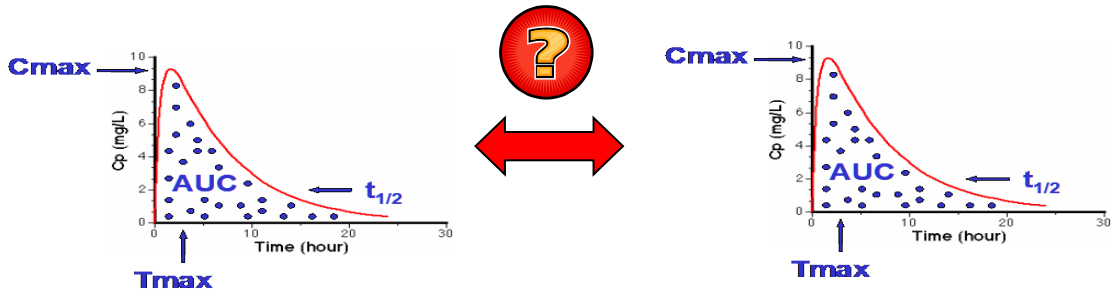
EMA, European Medicines Agency; FDA, Food and Drug Administration
EMA and FDA submission information available from company press releases (see notes page for citation details)

*Positive CHMP opinion received September 15, 2017
ABP 980 is an investigational product

MoAB's & Biosimilars

➲ Generic Drugs

- Bioequivalence is mandatory! Guidelines EMEA 01.2010



princeps *Generic drug*

- Singe dosing (repeated dosing is possible under some circumstances).
- n≥ 12 healthy volunteers, possible cross-over.
- AUC 0-72h, Tmax, Cmax .
- Food effect, DDI and other are strictly controlled.

➲ **Biosimilar ≠ Generic!**

Generics *VS.* Biosimilars

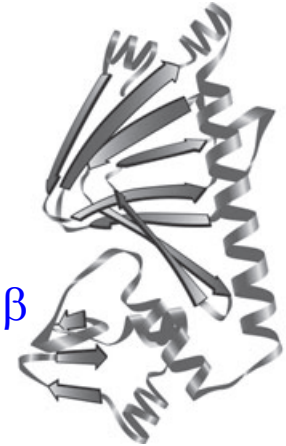
- Unlike generics, biologics and biosimilars are:
  - Structurally Complex
  - Tricky to characterize
  - Closely depending on the manufacturing process
  - Drugs whom efficacy or toxicity is modified by 3D structure

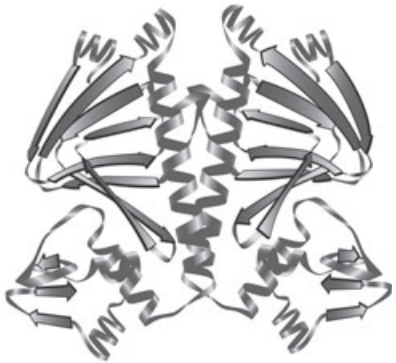
- **Guidelines for generic drugs do not apply to Biosimilars!**

Generics *VS.* Biosimilars

Primary : helix α

Secondairy : feuillet β





Quaternairy : dimere

Tertiairy : monomere

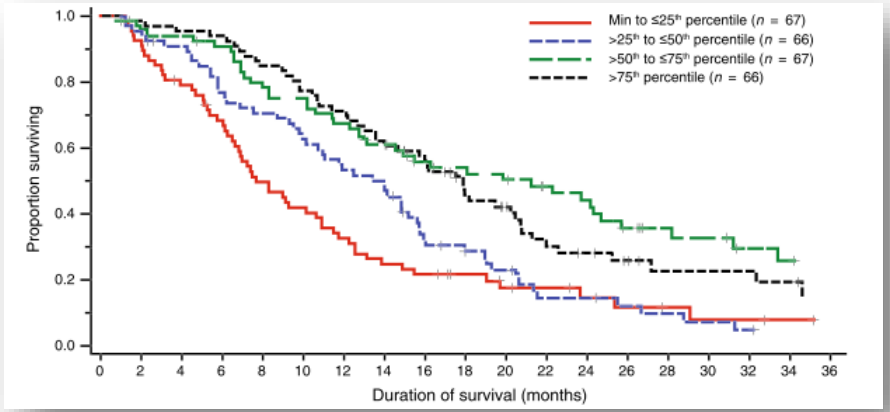
3D STRUCTURE MATTERS!
GLYCOSYLATION RATE MATTERS!

Generics *VS.* Biosimilars

- Active compounds:
  - Several different isoforms of proteins
  - Hard to reproduce when whange in manufacturing process
  - Analytical and quality control tricky to perform
- Need for clinical trials showing clinical equivalence… not PK equivalence!
- « Safety » : risk for increase in immunogenicity!

Generics *VS.* Biosimilars

- Lack for PK bioequivalence can have impact on pharmacodynamic endpoints (efficacy, safety)
- PK/PD of biologics is as important as PK/PD of small drugs!



Generics *VS.* Biosimilars

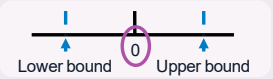
- ‘Minimally Clinically Important Difference’ (MCID)

Risk difference (RD)

Confidence interval for the **absolute difference** in primary endpoint between biosimilar and reference product

% biosimilar – % reference product

- If drugs have same efficacy, risk difference = 0



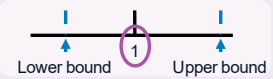
EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Risk ratio (RR)

Confidence interval for the **ratio** of primary endpoint for biosimilar versus reference product

$$\frac{\%\ \text{biosimilar}}{\%\ \text{reference product}}$$

- If drugs have same efficacy, risk ratio = 1

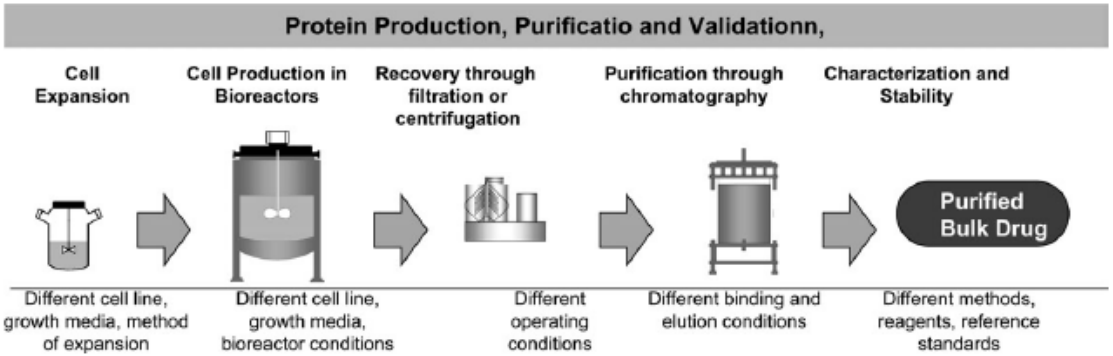


FDA

Biosimilar ≠ Biobetter!

Unlike generic drugs, no PK bioequivalence with princeps!

Differences in manufacturing process!

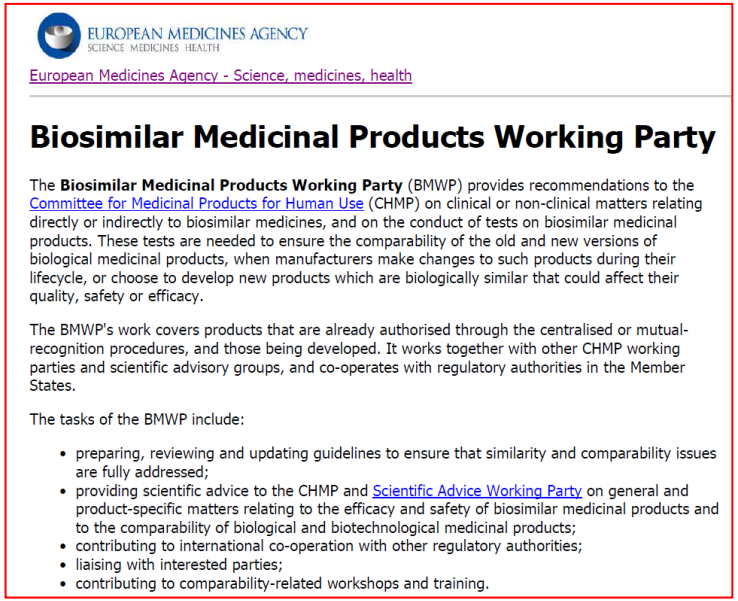


- AA sequence identical but:
  - 3D structure
  - Glycosylation profile
  - Manufacturing
- Makes PK change with subsequent possible impact on efficacy, safety (immunogenicity)

Mellstedt, Ann Oncol, 2008 **Roger, Expert Opin Biol Ther, 2010**

EMEA Guidelines

- Non clinical validation
  - *in vitro* and *in vivo* PK
  - Safety
- Clinical Efficacy
  - i.v. and s.c. routes
  - PK
  - PD
  - Biological Response
- Safety
  - i.v. and s.c. routes
  - Immunogenicity



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

European Medicines Agency - Science, medicines, health

Biosimilar Medicinal Products Working Party

The **Biosimilar Medicinal Products Working Party** (BMWP) provides recommendations to the Committee for Medicinal Products for Human Use (CHMP) on clinical or non-clinical matters relating directly or indirectly to biosimilar medicines, and on the conduct of tests on biosimilar medicinal products. These tests are needed to ensure the comparability of the old and new versions of biological medicinal products, when manufacturers make changes to such products during their lifecycle, or choose to develop new products which are biologically similar that could affect their quality, safety or efficacy.

The BMWP's work covers products that are already authorised through the centralised or mutual-recognition procedures, and those being developed. It works together with other CHMP working parties and scientific advisory groups, and co-operates with regulatory authorities in the Member States.

The tasks of the BMWP include:

- preparing, reviewing and updating guidelines to ensure that similarity and comparability issues are fully addressed;
- providing scientific advice to the CHMP and Scientific Advice Working Party on general and product-specific matters relating to the efficacy and safety of biosimilar medicinal products and to the comparability of biological and biotechnological medicinal products;
- contributing to international co-operation with other regulatory authorities;
- liaising with interested parties;
- contributing to comparability-related workshops and training.

http://www.ema.europa.eu

Trastuzumab

MABS
2017, VOL. 9, NO. 4, 704–714
http://dx.doi.org/10.1080/19420862.2017.1305530

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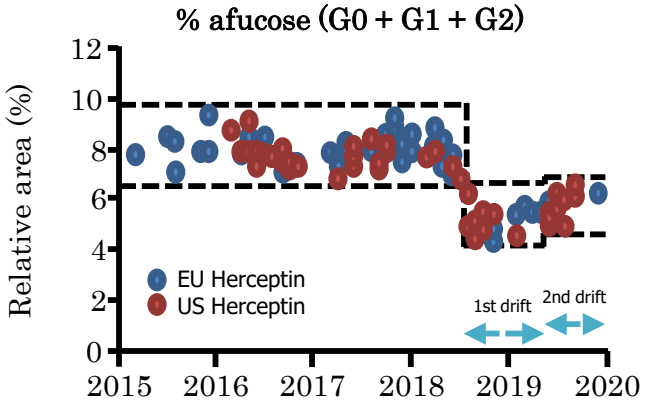
REPORT

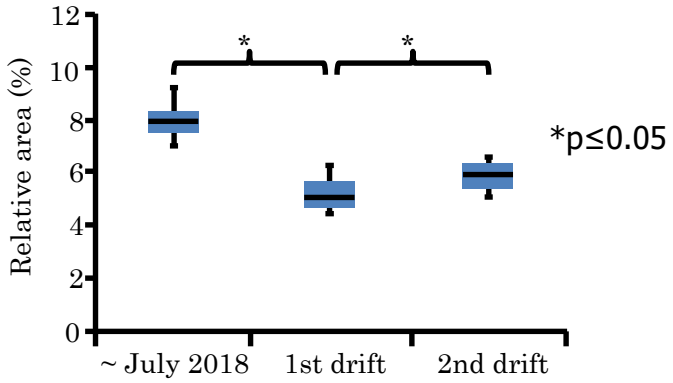
OPEN ACCESS

Drifts in ADCC-related quality attributes of Herceptin®: Impact on development of a trastuzumab biosimilar

Seokkyun Kim*, Jinsu Song*, Seungkyu Park, Sunyoung Ham, Kyungyeol Paek, Minjung Kang, Yunjung Chae, Heewon Seo, Hyung-Chan Kim, and Michael Flores

Downward drift in % afucose (G0±G1±G2) observed (EU + US reference product).





Kim S, et al. mAbs 2017

Trastuzumab

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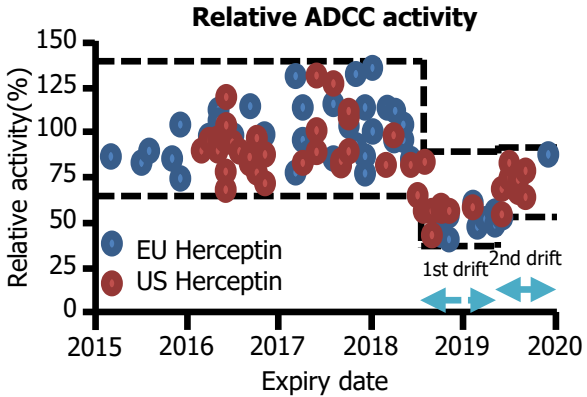
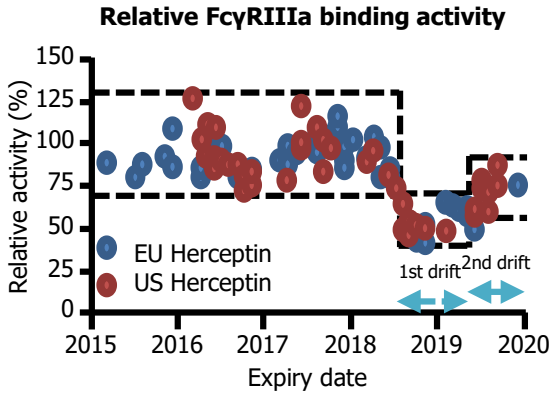
Impact of drifts on ADCC and FcγRIIIa binding





Levels of % afucose and % high mannose should be tightly monitored as critical quality attributes for biosimilar development of trastuzumab!

Kim S, et al. mAbs 2017

Trastuzumab

MABS
2017, VOL. 9, NO. 4, 704–714
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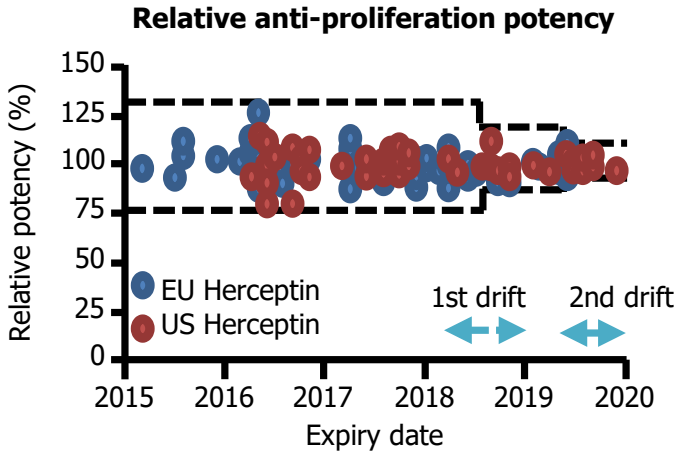
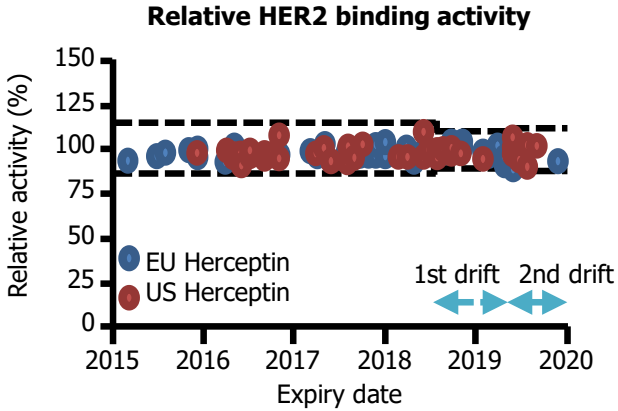
Impact of drifts on anti-proliferative potency and HER2 binding activity



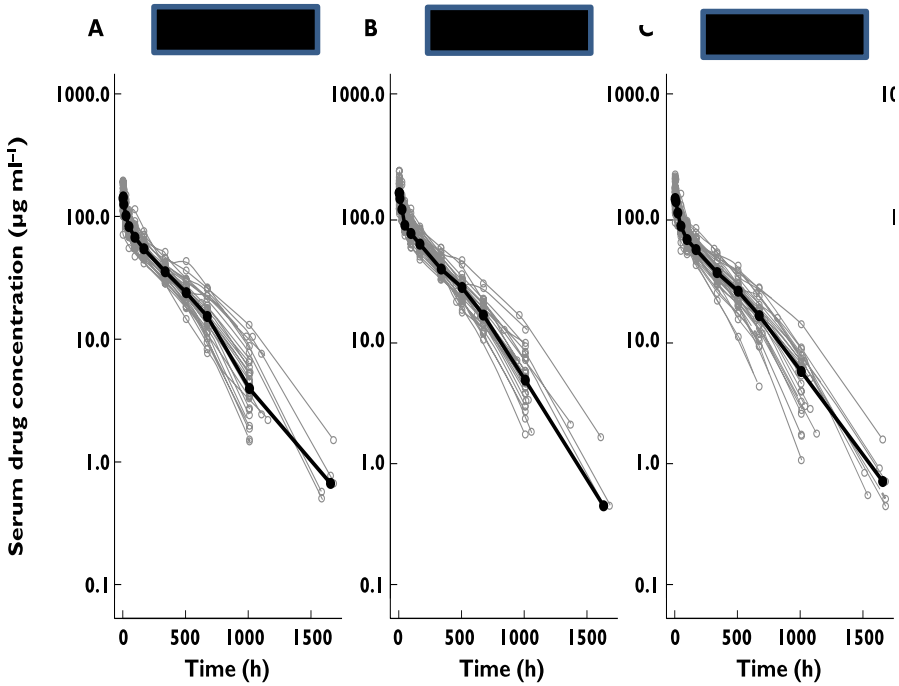


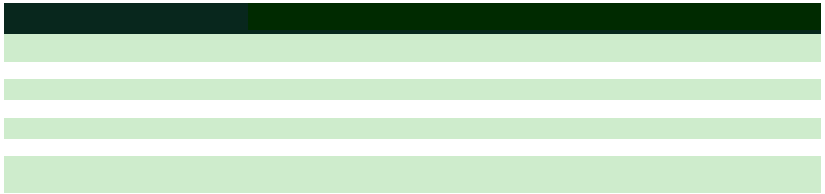
Clinical relevance can be questionned!

Kim S, et al. mAbs 2017

Trastuzumab Biosimilar: should we be afraid of PK?

Randomised Phase 1 PK trial comparing potential biosimilar PF-05280014 with trastuzumab in healthy volunteers (REFLECTIONS B327-01)[1]





Yin D, et al. Br J Clin Pharmacol 2014;78:1281–9;
Pivot X, et al. Clin Ther 2016;38:1665–1673.e3

Trastuzumab Biosimilar: should we be afraid of PK?

Randomised Phase 1 PK study comparing biosimilar candidate SB3 and trastuzumab in healthy male subjects[2]

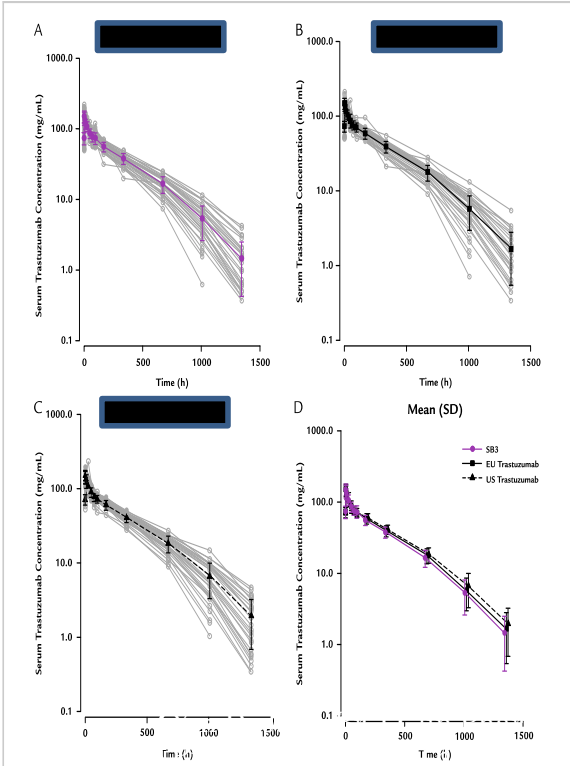


Table II. Summary statistics of pharmacokinetic parameters after a single dose of 6 mg/kg in healthy male subjects.*

Statistic			
$AUC_{0-\infty}$, μg · h/mL	34,783 (5614)	35,890 (5761)	37,370 (5620)
AUC_{0-last}, μg · h/mL	34,321 (5349)	35,368 (5524)	36,690 (5342)
C_{max}, μg/mL	154 (28)	153 (25)	156 (26)
T_{max}, median (range), h	1.58 (1.52-95.95)	1.61 (1.53-48.07)	1.57 (1.53-24.03)
$t_{1/2}$, h	196 (45)	198 (42)	215 (53)
CL, mL/h	13.83 (2.10)	13.52 (2.43)	12.82 (2.24)
C_{day21}, μg/mL†	23.4 (4.6)	25.0 (5.7)	25.0 (6.4)

Yin D, et al. Br J Clin Pharmacol 2014;78:1281–9;
Pivot X, et al. Clin Ther 2016;38:1665–1673.e3

Trastuzumab Biosimilar: should we be afraid of PK?

Seems that U.S. and E.U. princeps were more PK'ally different than biosimilar and princeps!

TAKE HOME MESSAGE

- ✓ PK and PK/PD considerations with Mabs are critical.
- ✓ Biosimilars are not generic drugs.
- ✓ Differences in PK could lead to substantial changes in clinical activity.

- ✓ Differences in PK between biosimilars and princeps can be smaller than differences among princeps!