# Considerations for Biologics and Non-Biological Complex Drugs

Daan J.A. Crommelin

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**SESSION 1: COMPLEX GENERICS - CHALLENGES AND OPPORTUNITIES**

Moderator: *Wenlei Jiang, FDA*

**Gottlieb: Changes To Hatch-Waxman May Boost Complex Generic Market**

April 04, 2019

Outgoing FDA chief Scott Gottlieb pinpointed complex generic and second-to-market novel drug development as two key areas in which he thinks the agency could have an effect in the drug pricing arena. During a House Appropriations subcommittee hearing on Wednesday (April 3), he told lawmakers they could contemplate changes to Hatch-Waxman that would allow the agency to look at small complements of clinical data when approving generics of complex drugs, and he highlighted that a lack of financial incentives are holding companies back from developing second-to-market novel drugs.

InsideHealthPolicy, 4 April 2004

# Considerations for Biologics and Non-biological Complex Drugs (NBCDs)

- Introduction: Complex drugs……. A multifaceted landscape
- A glance at the regulatory framework for biosimilars
- CQA assessment, comparability, evolution, drift and divergence
- Formulation: freedom to operate, does it make a/the difference?
- Market penetration in the EU, consequences
- **Non-**Biological Complex Drugs (NBCD): similarity with biosimilars….. Published dissimilarity observed outside the USA. Present regulatory schemes. How to proceed?
- Conclusions

# The complex drug –many nanomedicines- landscape (an impressionist view)

challenging

Small molecule
Biologics
NBCDs (incl. nanoparticles*)
Other Complex Drugs

Demonstration of Pharmaceutical equivalence (PE)

Iron sucroses*
Glatiramoids*
Albumin-bound nanoparticles *
Swelling cross-linked polymers
MABs
FSH
IFN ß
Liposomes, dendrimers & polymeric micelles*
LMWHs*
Ocular emulsions*
INS
GH
epo
Small molecule drugs
Narrow therapeutic index drugs
Topical drug products
Inhalers

simple → challenging

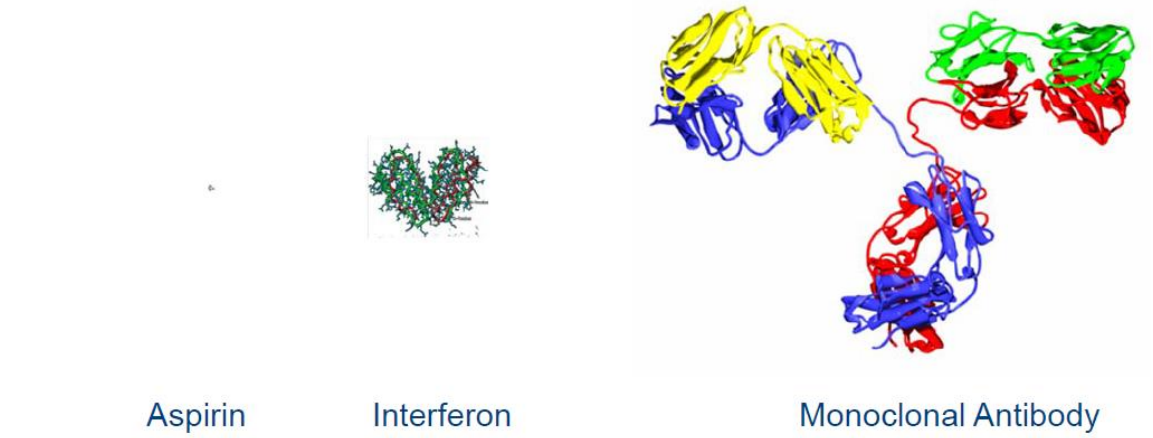
Demonstration of Bioequivalence (BE)

**PE + BE = TE**

Adapted from Hussaarts et al. Annals of the NYAS 2016

# Small molecules versus proteins: size difference

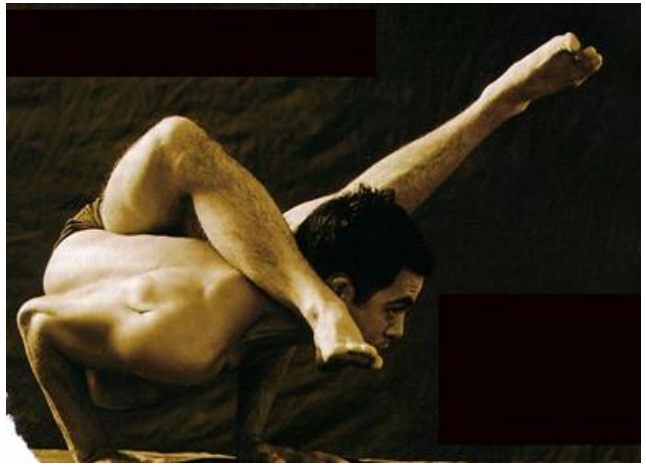
## Proteins are ….. Big!



Aspirin Interferon Monoclonal Antibody

Mw around 150 around 20,000 around 150,000

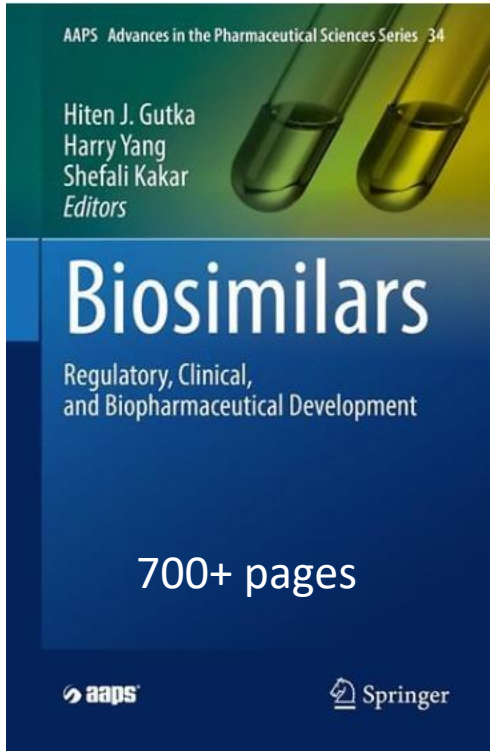

## Proteins are ‘vulnerable’



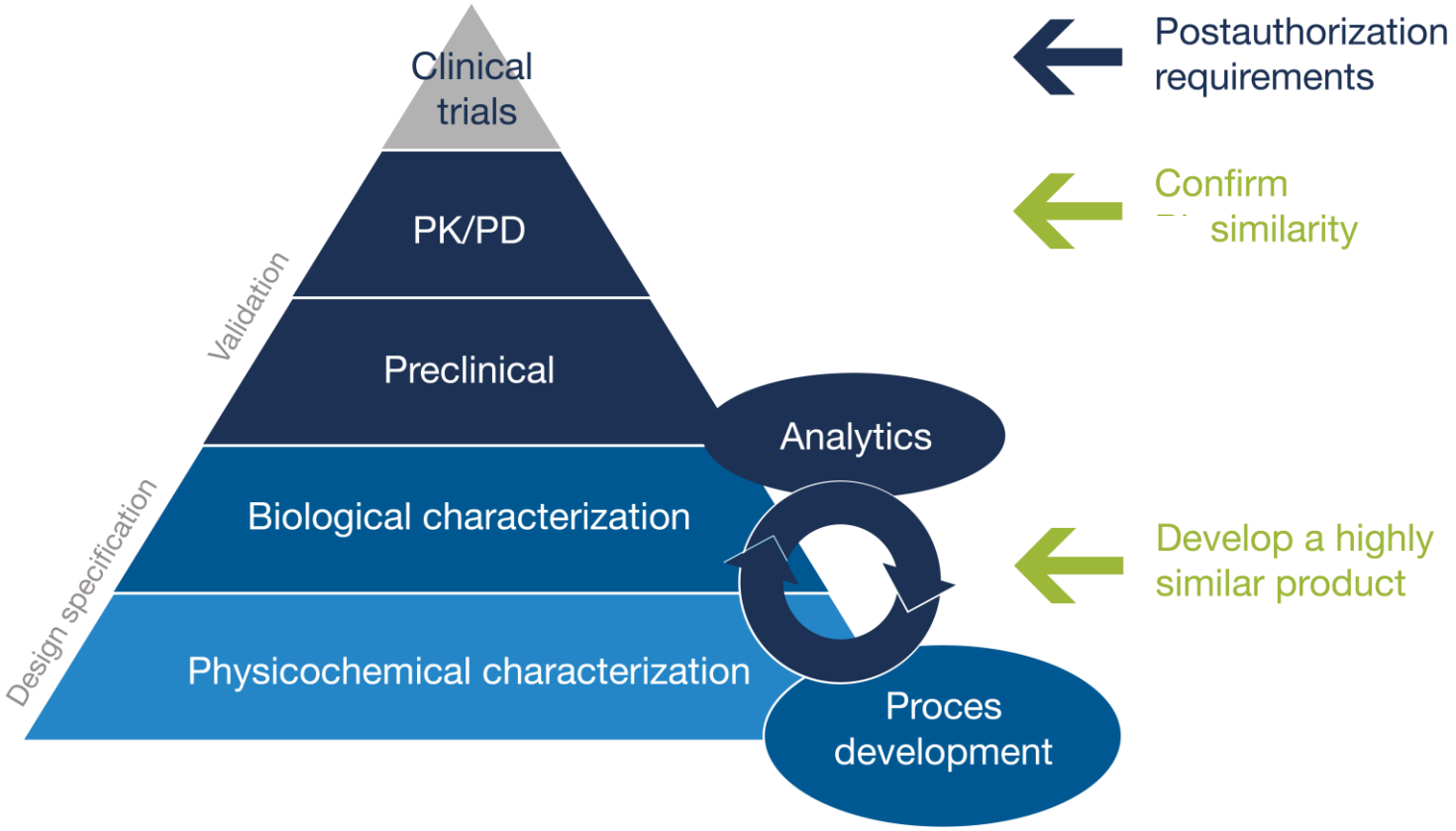
# How do Biologics compare to small, low molecular weight drugs?

| | SMALL MOLECULE DRUGS | BIOLOGICS |
|---|---|---|
| **Molecular weight** | Low (<500) | High (range 5-900 kDa) |
| **Structure** | Simple, well-defined | Complex, heterogeneous, defined by manufacturing process |
| **Modifications** | Well-defined | Many options |
| **Manufacturing** | Chemical synthesis | Produced in living cells or organisms |
| **Stability** | Stable | Generally unstable, sensitive to external conditions |
| **Immunogenicity** | Mostly non-immunogenic | Mostly immunogenic |
| **Copy characteristics** | Identical copies can be made | Impossible to ensure identical copy versions |

*Adapted from GaBI Online – Generics and Biosimilars Initiative [www.gabionline.net/Biosimilars/Research/Small-molecule-versus-biological-drugs](www.gabionline.net/Biosimilars/Research/Small-molecule-versus-biological-drugs), based on Declerck and Schellekens.*




# Complex Drug Development Process? A stepwise approach – totality of evidence




Proving "highly similar" to reference product often requires multiple iterations to optimize process as assessed by physico-chemical characterization

*Adapted from McCamish and Woollet;* MAbs. 2011 Mar-Apr;3(2):209-17.

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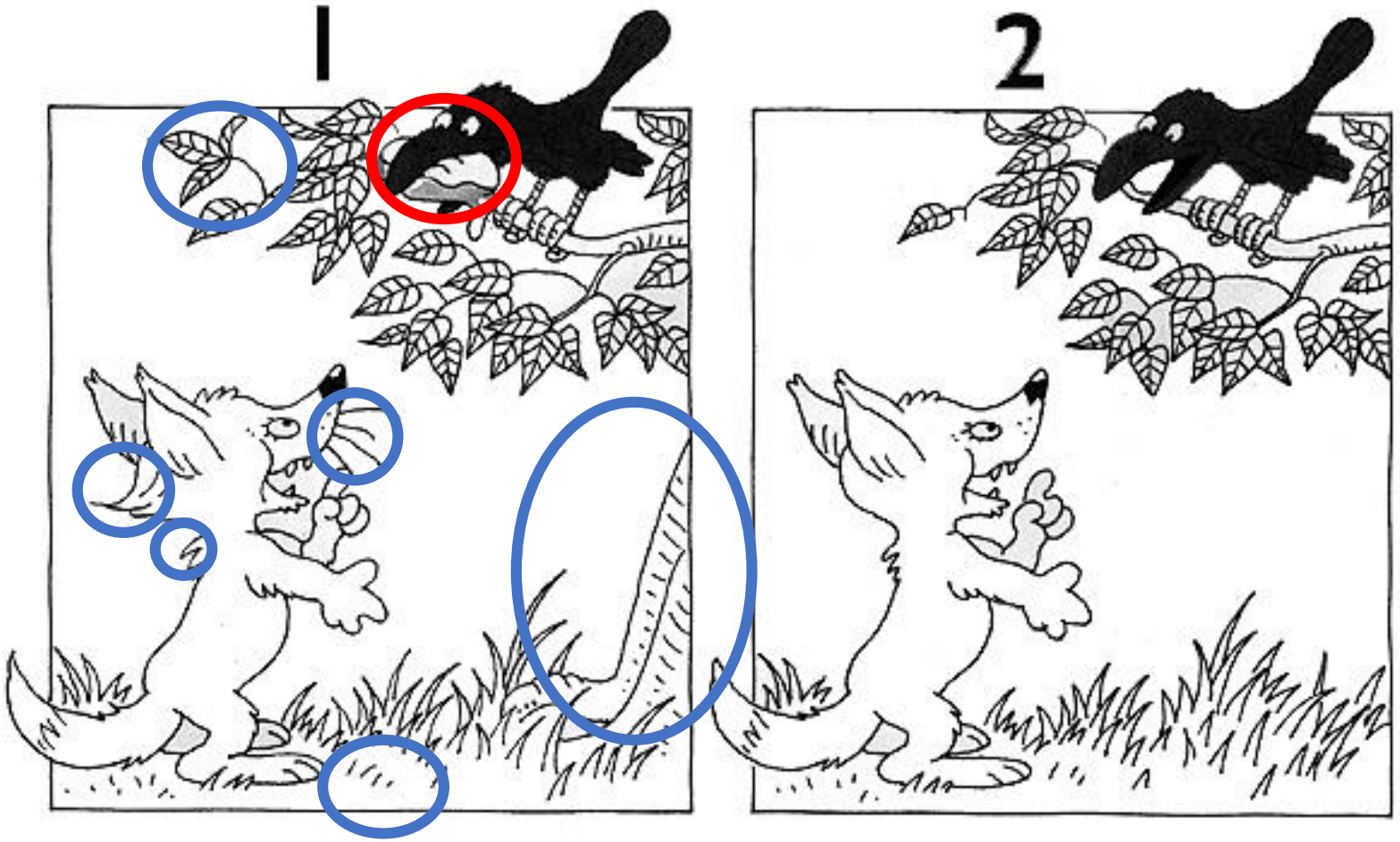
# Similarity……Critical Quality Attributes (CQA): what counts?




From Wim-Jiskoot

A-Mab: a Case Study in Bioprocess Development

CMC Biotech Working Group

Pfizer · MedImmune · Genentech (A Member of the Roche Group) · Lilly · Abbott · GlaxoSmithKline · Amgen


# Experience with a group of complex drugs: CQA analysis of MABs

## 278 pages

**Table 2.2 Typical Quality Attributes for a Monoclonal Antibody**

| Product Variants | | Purity (including Process-related impurities) | |
|---|---|---|---|
| Aggregation | Fragmentation | Microbiological Purity | Selective agent |
| Conformation | Glycation | Viral Purity | Cell Culture Medium Components |
| C-Terminal Lysine | Glycosylation | DNA | |
| Deamidated Isoforms | Oxidation | HCP (Host Cell Protein) | Purification Buffer Components |
| Disulfide Bonds | Thioether link | Protein A | |

| Drug Product Attributes | |
|---|---|
| Foreign Particles | pH |
| Clarity | Product Concentration |
| Color | Potency |
| Osmolality | Volume |

A-Mab: a Case Study in Bioprocess Development

CMC Biotech Working Group



**Table 2.29 Basis for Acceptable Ranges for the Quality Attributes Discussed in the Case Study**

| Attribute | Prior Knowledge | In-vitro Studies | Non-clinical Studies | Clinical Experience | Claimed Acceptable Range | Rationale for Claimed Acceptable Range |
|---|---|---|---|---|---|---|
| Afucosylation | 1-11%; Clinical experience with X-Mab and Y-Mab; both X-Mab and Y-Mab have ADCC as part of MOA | A-Mab with 2-13% afucosylation tested in ADCC assay; linear correlation; 70-130% | Animal model available; modeled material (15%) shows no significant difference from 5% | 5-10%; Phase II and Phase III | 2-13% | 2-13% afucosylation correlates with 70-130% ADCC activity. Lower end covered by prior knowledge; upper end covered by modeled material in animal model. |
| Aggregation | 1-5% aggregate (at end of SL) in clinical studies and commercial production with X-Mab; minimal ATAs with | Purified A-Mab dimer has similar biological activity to monomer | Animal models typically not relevant | 1-3% aggregate | 0-5% | 5% upper range claimed based on prior clinical experience with X-Mab. |
| HCP | Phase I trial (corresponds to 120 ng/mg HCP level) | NA | NA | 5-20 ng/mg | 0-100 ng/mg | on prior clinical experience with X-Mab. |
| Sialic Acid | Literature data show sialylated forms can impact PK and ADCC | Level of 0-2% on A-Mab shows no statistical correlation to ADCC | NA | 0-0.2%; Phase II and II | 0-2% | In vitro studies with A-Mab. |
| High Mannose | Literature data show afucosylated forms impact ADCC | NA | NA | 3-10%; | 3-10% | Clinical Experience with A-Mab. |
| Non-Glycosylated Heavy Chain | Literature data show that non-glycosylated forms impact ADCC | NA | NA | 0-3% | 0-3% | Clinical Experience with A-Mab. |

SAE = serious adverse event; SL = shelf life


| Attribute | Prior Knowledge | In-vitro Studies | Non-clinical Studies | Clinical Experience | Claimed Acceptable Range | Rationale for Claimed Acceptable Range |
|---|---|---|---|---|---|---|
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- **Design Space defined!**

# Models to assess ‘criticality’…..

From the A mab case
Assessment of *criticality*
Ranking….. A tool from the  toolbox: ***impact x uncertainty***
(tool 1, A mab study)

*The AAPS Journal* (2018) 20:68
DOI: 10.1208/s12248-018-0250-9

*White Paper*

**Rational Selection, Criticality Assessment, and Tiering of Quality Attributes and Test Methods for Analytical Similarity Evaluation of Biosimilars**

Kristof Vandekerckhove,[1] Andreas Seidl,[2] Hiten Gutka,[3] Manish Kumar,[4] Gyöngyi Gratzl,[5] David Keire,[6] Todd Coffey,[7] and Henriette Kuehne[8,9]

Analytical toolbox

# Quality attributes and test methods used for physicochemical and biological similarity assessment between Herceptin and a biosimilar

Table 2. Quality Attributes and Test Methods used for Physicochemical and Biological Similarity Assessment between CT-P6 and Herceptin®.

| Attribute | | Risk Ranking | Test/Assay | Measurement | Tier of Statistical Analysis |
|---|---|---|---|---|---|
| Primary Structure | Primary Amino Acid Sequence | High | Molar Absorptivity | Molar absorptivity/ Extinction coefficient | 2 |
| | | | Peptide Mapping (HPLC) | Peak profile | 3[1] |
| | | | Peptide Mapping (LC-MS) | Peak profile | 3[1] |
| | | | N-terminal Sequencing | Sequence identity | 3[1] |
| | | | C-terminal Sequencing | Sequence identity | 3[1] |
| Post Translational Modifications | Deamidation | Moderate | Peptide Mapping (LC-MS) | % Deamidation (Asn) | 2 |
| | Oxidation | Low | Peptide Mapping (LC-MS) | % Oxidation (Met) | 3 |
| | Isomerization | Moderate | Peptide Mapping (LC-MS) | % Isomerization (Asp) | 2 |
| | | | ing (LC-MS) | % N-terminal glutamine | 3 |
| | | | ing (LC-MS) | % C-terminal lysine | 3 |
| | | | ing (LC-MS) | % C-terminal proline amidation | 3 |
| | | | duced Peptide | Disulfide bond positions | 3 |
| | | | lysis | Free thiol (SH groups) | 2 |
| | | | | Structure of protein by spectroscopy | 3[1] |
| | | | | a-helical, b-sheet and unordered structures | 3[1] |
| | | | | Thermal unfolding temperatures | 2 |
| | | | y | 3D conformational epitope exposure | 3[1] |
| | | | | % Monomer content | 2 |
| | | | | % HMW Content | 2 |
| | | | | Monomer size (kDa) | 2 |
| | | | | HMW size (kDa) | 3[2] |
| | | | | % Monomer content | 2 |
| | | | | % HMW content | 2 |
| | | | | Monomer S value | 2 |
| | | | | Dimer S value | 2 |
| | | | | % Monomer content | 2 |
| | | | | % Dimer content | 2 |
| | | | CE-SDS | % Intact IgG | 2 |
| | | | | % Sum of non-Assembled Fragments | 2 |
| | | | Cell Protein ELISA | HCP (ppm) | 3 |
| | | | Cell DNA PCR | | |
| | | | ein A ELISA | | |
| Charge Variants | Charge Variants | Moderate (Deamidated/ Isomerization) | IEF | | |
| | | Very Low (All others) | IEC-HPLC | % Peak 1+Peak 2+Peak 3+Peak 4 | 2 |
| | | | | % Peak 6 | 2 |
| | | | | % Peak 5 | 3 |
| | | | | % Peak 7 | |
| Glycosylation | Non-glycosylated Product | Moderate | Reduced CE-SDS | % Non-glycosylated Heavy Chain % L+H | 2 |
| | Afucosylated Glycans | Moderate | Oligosaccharide Profiling | %G0+G1+G2 | 2 |
| | | | N-linked Glycan Analysis | %G0+G1+G2 | 2 |
| | High Mannose Glycans | Moderate | Oligosaccharide Profiling | %Man5+Man6+ Man8 | 2 |
| | | | N-linked Glycan Analysis | %Man5 | 2 |

Analytical toolbox

Table 2. (*Continued*).

| Attribute | | Risk Ranking | Test/Assay | Measurement | Tier of Statistical Analysis |
|---|---|---|---|---|---|
| | Sialic Acids | Low | Oligosaccharide Profiling | %[G1F-GN+NANA]+[G1F+NANA]+[G2F+NANA]+[G2F+2NANA] | 3 |
| | | | Sialic Acid Analysis | NANA (sialic acid / protein, mol / mol) | 3 |
| | Glycation | Low | Glycation analysis | % Glycation at light chain<br>% Glycation at heavy chain | 3 |
| Fab Binding | HER2 Binding | Very High | HER2 Binding Affinity (ELISA) | Relative HER2 Binding (%) | 2[3] |
| | | | Cell-based HER2 Binding Affinity (CELISA) | | 2[3] |
| | Anti-proliferation | Very high | In Vitro Bioactivity (anti-proliferation) using BT-474 Cell | Relative Anti-proliferation (%) | 1 |
| Fc Binding | C1q Binding | Low | C1q Binding (ELISA) | Relative C1q Binding (%) | 3 |
| | FcγRIIIa Binding | High | FcγRIIIa V Type Binding Affinity (SPR) | Relative FcγRIIIa V Type Binding Affinity (%) | 2 |
| | | | FcγRIIIa F Type Binding Affinity (SPR) | Relative FcγRIIIa F Type Binding Affinity (%) | 2 |
| | FcγRIIIb Binding | Moderate | FcγRIIIb Binding Affinity (SPR) | Relative FcγRIIIb Binding Affinity (%) | 2 |
| | FcγRIIa Binding | High | FcγRIIa Binding Affinity (SPR) | Relative FcγRIIa Binding Affinity (%) | 2 |
| | FcγRIIb Binding | Moderate | FcγRIIb Binding Affinity (SPR) | Relative FcγRIIb Binding Affinity (%) | 2 |
| | FcγRI Binding | Low | FcγRI Binding Affinity (SPR) | Relative FcγRI Binding Affinity (%) | 3 |
| | FcRn Binding | Moderate | FcRn Binding Affinity (SPR) | Relative FcRn Binding Affinity (%) | 2 |
| Fab –Fc Mediated Activities | ADCC | Very High | ADCC (PBMC) | Relative ADCC Potency (%) | 1 |

[1]Tier 3 was assigned because nature of the assays is qualitative despite of "high" or "moderate" risk ranking.
[2]Tier 3 was assigned due to the trace amount of HMW content to precisely evaluate the molecular weight by MALS.
[3]Tier 2 was assigned considering HER2 binding affinity does not measure the MoAs (anti-proliferation or ADCC activities) directly relevant to the clinical efficacy of trastuzumab.

**Conclusion: assessment of similarity of a mab is using a large toolbox with orthogonal and complementary –looking at different aspects- test methods**

Jihun Lee, Hyun Ah Kang, Jin Soo Bae, Kyu Dae Kim, Kyoung Hoon Lee, Ki Jung Lim, Min Joo Choo, and Shin Jae Chang

Biotechnology Research Institute, R&D Division, Celltrion Inc., Incheon, Korea

REPORT

# Evaluation of analytical similarity between trastuzumab biosimilar CT-P6 and reference product using statistical analyses

Jihun Lee , Hyun Ah Kang, Jin Soo Bae , Kyu Dae Kim, Kyoung Hoon Lee, Ki Jung Lim, Min Joo Choo and Shin Jae Chang

Biotechnology Research Institute, R&D Division, Celltrion Inc., Incheon, Korea

MABS
2018, VOL. 10, NO. 4, 547–571
https://doi.org/10.1080/19420862.2018.1440170

Table 1. Risk ranking determination and tier classification.

| Potential Clinical Impact | | Degree of Uncertainty | | Risk Ranking | Tier |
|---|---|---|---|---|---|
| Very High, High, Medium, Low, Very Low | × | High, Medium, Low | = | Very High | 1 |
| | | | | High / Moderate | 2 |
| | | | | Low / Very Low | 3 |

| | Quality Attribute / Test Method |
|---|---|
| Tier 1<br>F(ab') related Activities[3] | Anti-proliferation |
| Fab-Fc Mediated Activities[3] | ADCC (%) |

Lee et al., 2018

MABS 2018, VOL. 10, NO. 4, 547–571
https://doi.org/10.1080/19420862.2018.1440170

**Comparison of charge variants (acidic and basic) of trastuzumab originator and biosimilar products**

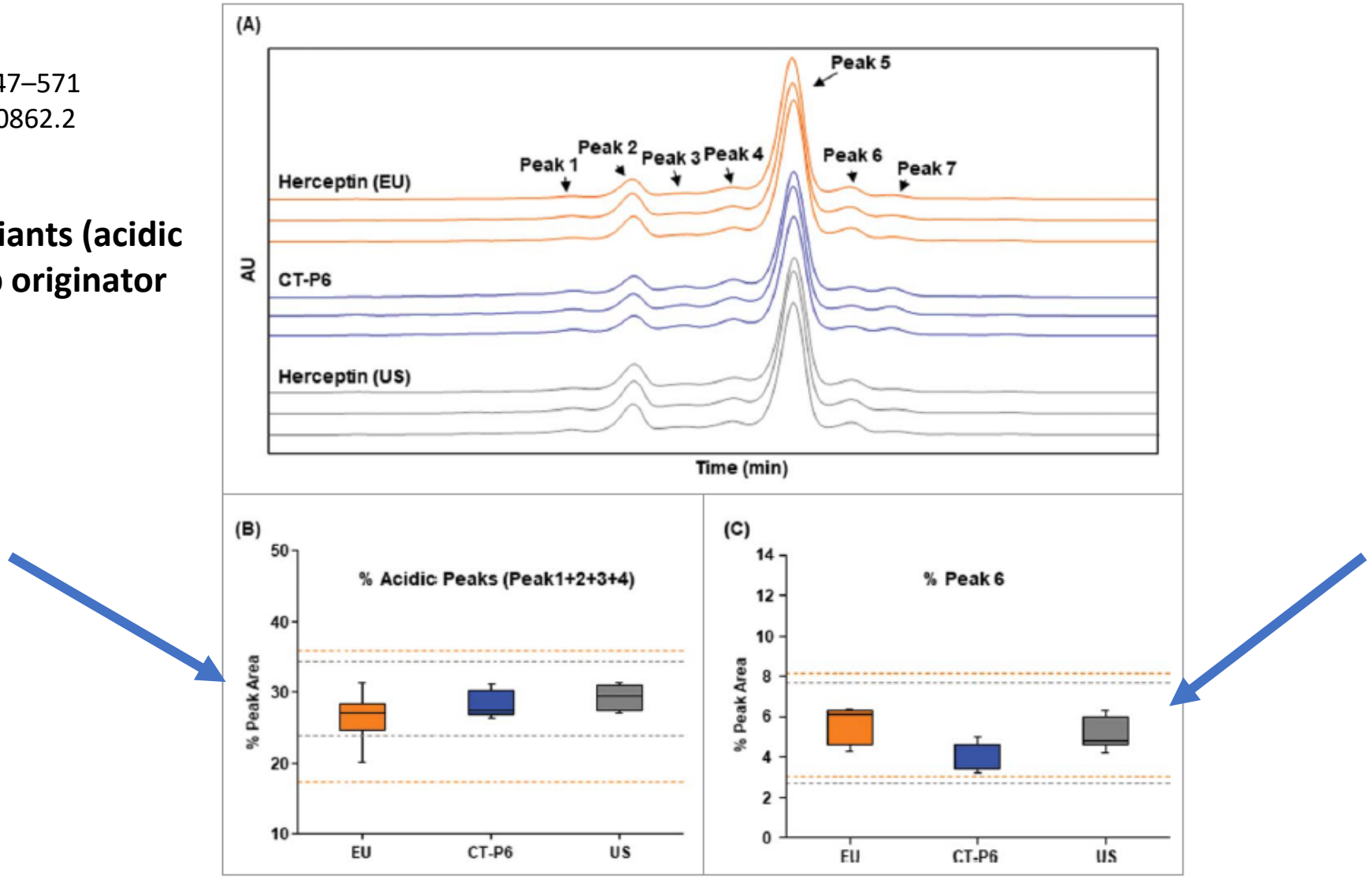
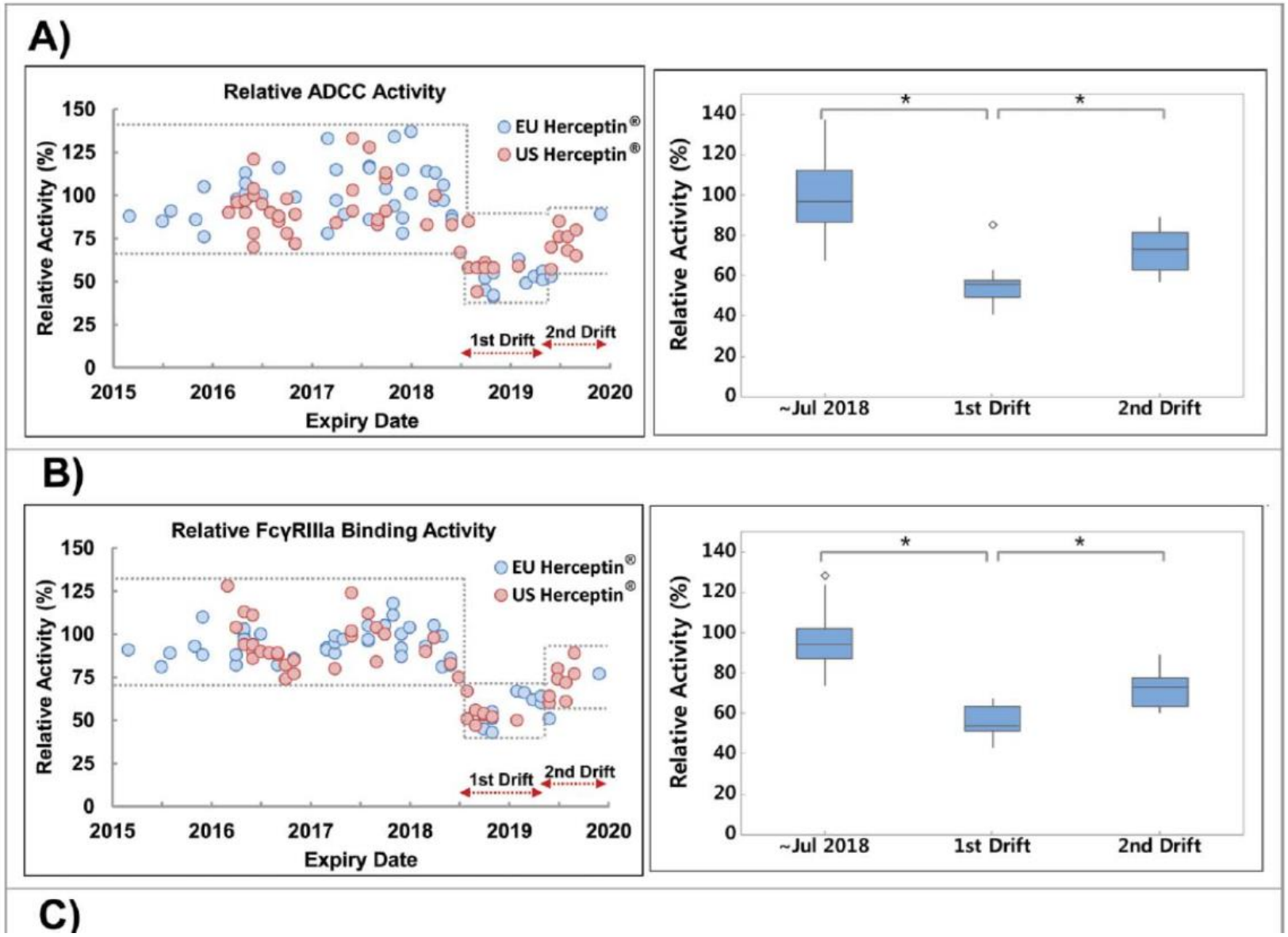



Figure 6. Comparison of charge variants of CT-P6 (blue), EU-Herceptin® (orange) and US-Herceptin® (grey) analyzed by IEC-HPLC. (A) Representative ion exchange chromatograms are presented for 3 batches of each product. The number and distribution of IEC-HPLC peaks are conserved between CT-P6 and RMPs. (B) Box plots of acidic peaks % (Peak 1 + Peak 2 + Peak 3 + Peak 4) in IEC-HPLC, (C) Box plot of Peak 6 % in IEC-HPLC. Orange and grey broken lines represent quality range of EU-Herceptin® and US-Herceptin®, respectively. Box plot shows the interquartile range (box), median (band inside of box), maximum and minimum values (whiskers).

# The innovator product drifts, from Lee et al., 2018



BioDrugs (2014) 28:363–372
DOI 10.1007/s40259-014-0088-z

REVIEW ARTICLE

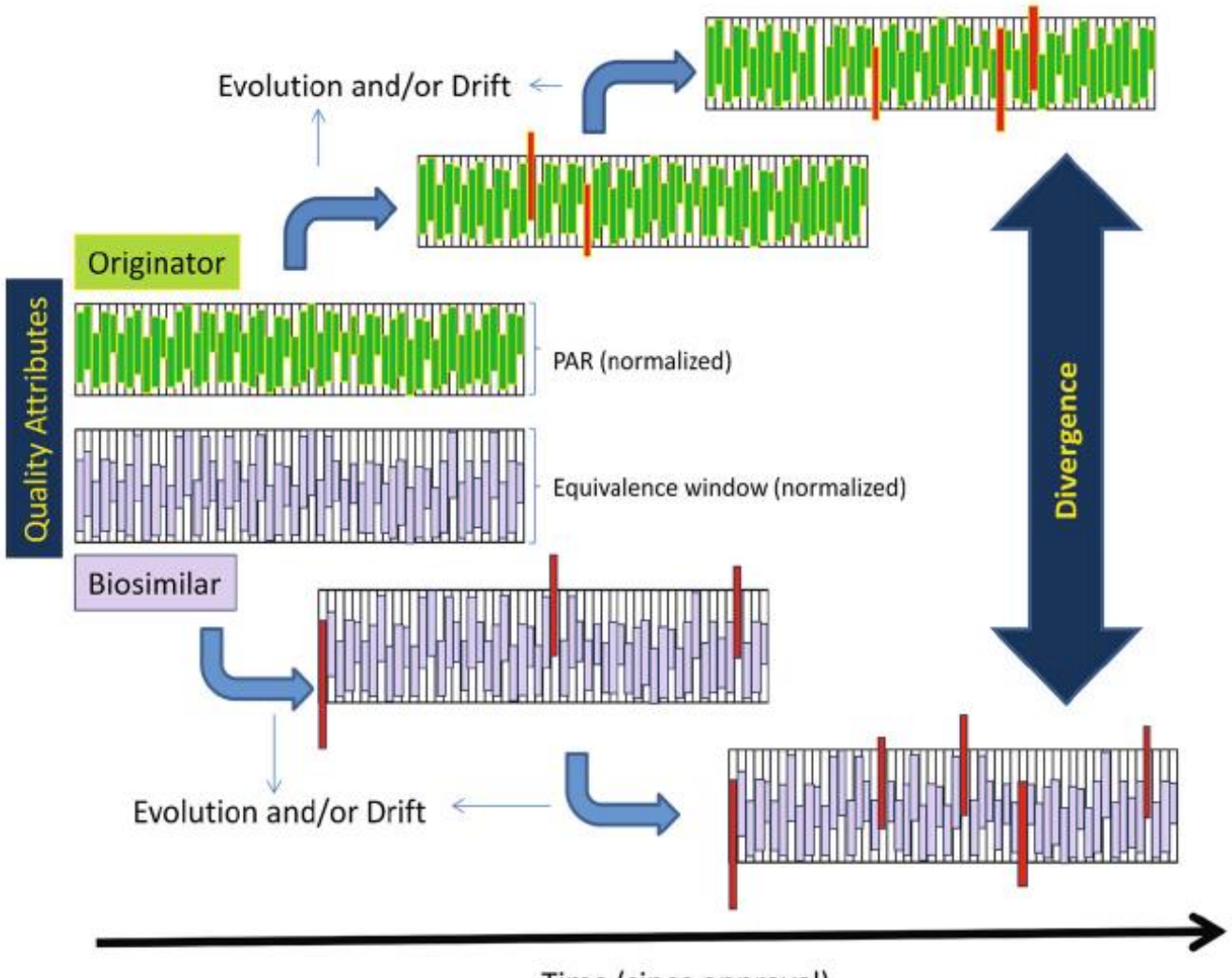
# Evolution and/or Drifting …….

**Drift, Evolution, and Divergence in Biologics and Biosimilars Manufacturing**

Sundar Ramanan · Gustavo Grampp



**Fig. 6** Post-licensure evolution and/or drift can lead to product divergence. *PAR* proven acceptable range




Herceptin®, trastuzumab
EMA: Procedural steps taken and scientific information after the authorisation: 145

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2017

# Basic information source: formulation differences


‘Some differences may be allowed if they have no effect on safety and efficacy - for example differences in the formulation of the medicine (e.g. excipients), presentation (e.g. powder to be reconstituted versus solution ready for injection)’.

# Humira and biosimilars in the EU

| | Humira® ('new') | Humira® ('classic') | Imraldi® | Amgevita™ | Cyltezo® | Hyrimoz® | Hulio® |
|---|---|---|---|---|---|---|---|
| Citrate | N | Y | Y | N | N | Y | N |
| Needle gauge | AI: 29<br>PFS: 29 | AI: 27<br>PFS: 27 | PFS: 29<br>AI: 29 | PFS: 29<br>AI: 27 | PFS: 27<br>AI: 27 | PFS: 27<br>AI: 27 | AI:20<br>PFS:29 |
| Latex* | N | Y | N | Y | Y | Y | N |
| pH | 5.2† | 5.2 | 5.2 | 5.2 | 5.2 | 5.2 | 5.2 |
| Volume (mL) | 0.4 | 0.8 | 0.8 | 0.8 | 0.8 | 0.8 | 0.8 |
| Complete formulation | Mannitol, Polysorbate 80, WFI | Mannitol, Polysorbate 80, Sodium hydroxide, Citric acid monohydrate, Sodium citrate, Sodium dihydrogen, phosphate dihydrate, Disodium phosphate dihydrate, Sodium chloride, WFI | Sorbitol, Polysorbate 20, Sodium citrate, Citric acid monohydrate, Histidine, Histidine hydrochloride monohydrate, WFI | Sucrose, Polysorbate 80, Glacial acetic acid, Sodium hydroxide (pH), WFI | Trehalose dihydrate, Polysorbate 80, Glacial acetic acid, Sodium acetate trihydrate, WFI | Mannitol, Polysorbate 80, Adipic acid, Citric acid monohydrate, Sodium chloride Hydrochloric acid (pH) Sodium hydroxide (pH) WFI | Sorbitol, Polysorbate 80, Monosodium glutamate, Methionine, Hydrochloric acid (pH) WFI |
| **Approved shelf life** | 2 years | 2 years | 3 years | 2 years | 2 years | 2 years | 2 years |
| **Room temp stability** | maximum of 25°C for a period of up to 14 days (except vial) | maximum of 25°C for a period of up to 14 days | maximum of 25°C for a period of up to 14 days* (28 days published) | maximum of 25°C for a period of up to 14 days | maximum of 25°C for a period of up to 14 days | maximum of 25°C for a period of up to 14 days | maximum of 25°C for a period of up to 14 days |

**In the Netherlands in December 2018 a 80% price drop of Humira, savings 180 million euros in the NL**

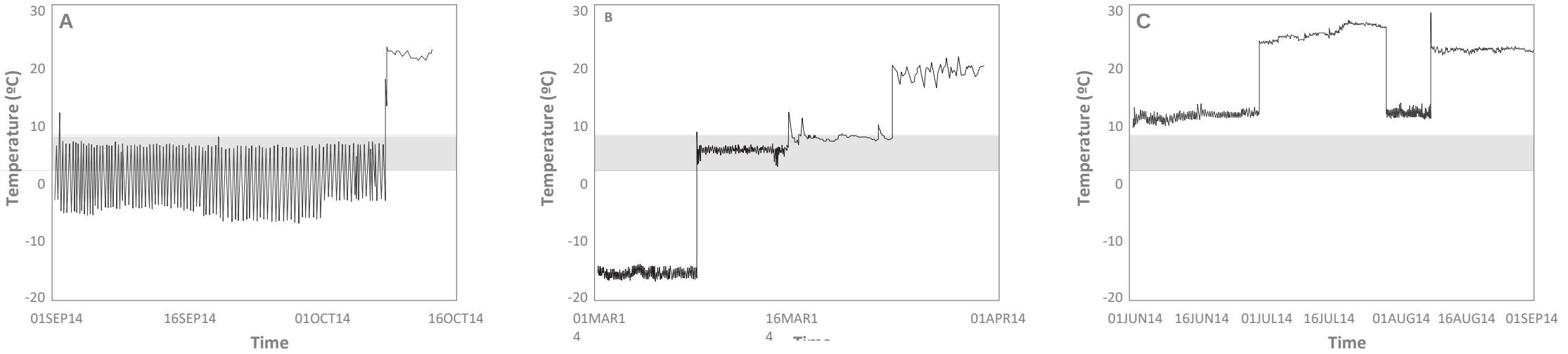
From Hans Ebbers, 2018

# Product stability is critical: many patients do not store biologics correctly

Only 6.7% of the patients stored all bDMARDs packages within the defined SmPC-recommended temperature range

24.3% of patients stored their bDMARD for more than 2 hours consecutive time below 0°C and 2.0% for more than 2 hours above 25 °C

**Examples of deviation patterns among patients who did not store bDMARDs within the SmPC-recommended temperature range**




SmPC-recommended temperature range depicted by the horizontal green bars

Survey on transportation and storage of biological therapies by patients

Europ. J. Rheumatology 2019

Maira Arias Saavedra, Carolina Aimo, Jose Astudillo Andrade, Damaris Alvarez, Gabriel Sequeira, Eduardo Kerzberg

Vlieland et al. Rheumatology 2016;55:704-709

From Ebbers

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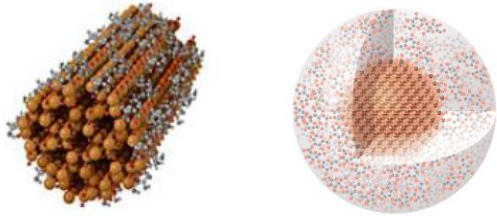
# What is are NBCDs = Non-Biological Complex Drugs

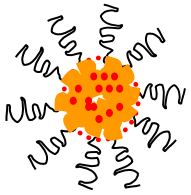
## A non-biological complex drug…

- … is a synthetic medicinal product that is **not a biological medicine**
- … with an active substance that is **not homo-molecular** but contains different (closely related, often nano-particulate) structures
- … that **cannot be fully characterized** by physicochemical analytical means.

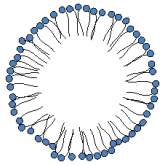
A **well-controlled** robust manufacturing process is fundamental to ensure quality, safety and efficacy.



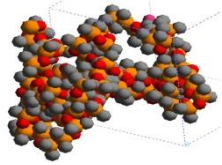
*Iron-carbohydrate complexes*



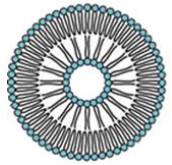
*Micelles*



*Nanoemulsions*



*Polymers*



*Liposomes*

*Dendrimers*

Full definition NBCD:Crommelin et al. Different pharmaceutical products need similar terminology; AAPS J. 2014

# The complex drug –many nanomedicines- landscape (an impressionist view)




**PE + BE = TE**

Adapted from Hussaarts et al. Annals of the NYAS 2016

# What is an NBCD? (1)

NBCDs are used to treat a **variety of serious medical conditions** including cancer, auto-immune diseases, infectious diseases, anemia, and more.


**Doxorubicin liposomes**
- Cancer
- Originator: Doxil® (Janssen)


**Glatiramer acetate**
- Multiple sclerosis
- Originator: Copaxone® (Teva Pharmaceuticals)

**Cyclosporine ophthalmic emulsion**
- Chronic dry eye disease
- Originator: Restasis® (Allergan)


**Iron sucrose**
- Anemia
- Originator: Venofer® (Vifor Pharma)

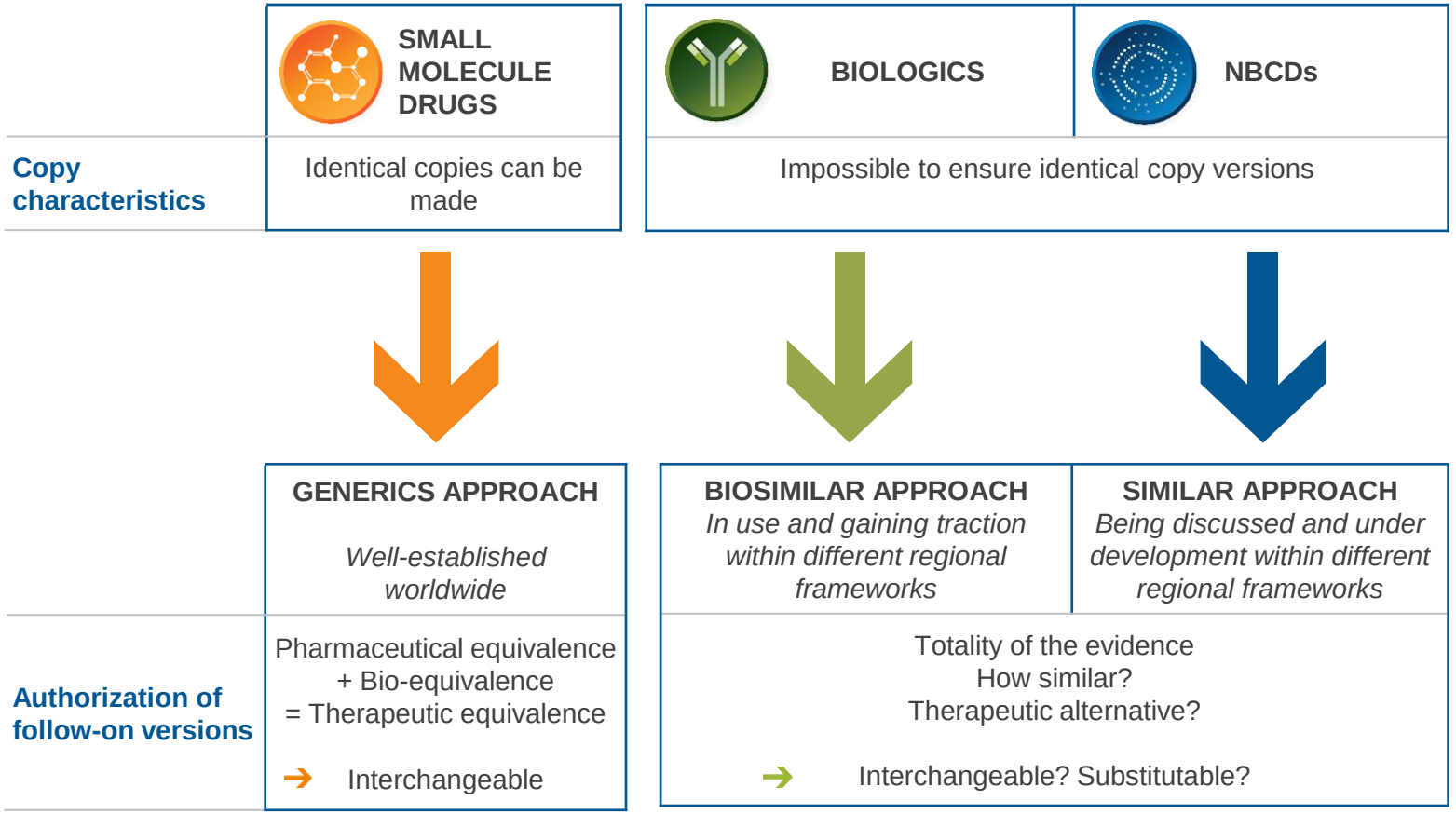

**Sevelamer carbonate**
- Control of phosphorus levels (chronic kidney disease)
- Originator: Renvela® (Sanofi)

# How do NBCDs compare to other drugs?

| | SMALL MOLECULE DRUGS | BIOLOGICS | NBCDs |
|---|---|---|---|
| **Molecular weight** | Low (<500) | High (range 5-900 kDa) | |
| **Structure** | Simple, well-defined | Complex, heterogeneous, defined by manufacturing process | |
| **Modifications** | Well-defined | Many options | |
| **Manufacturing** | Chemical synthesis | Produced in living cells or organisms | Synthetic technologies *(incl. nanotech)* |
| **Stability** | Stable | Generally unstable, sensitive to external conditions | |
| **Immunogenicity** | Mostly non-immunogenic | Mostly immunogenic | Immunogenicity varies |
| **Copy characteristics** | Identical copies can be made | Impossible to ensure identical copy versions | |

*Adapted from GaBI Online – Generics and Biosimilars Initiative [www.gabionline.net/Biosimilars/Research/Small-molecule-versus-biological-drugs](www.gabionline.net/Biosimilars/Research/Small-molecule-versus-biological-drugs), based on Declerck and Schellekens.*

# The similarity approach for biologics and many NBCDs




*Based on Schellekens et al; Regul Toxicol Pharmacol. 2011 Feb;59(1):176-83.*

European Journal of Pharmaceutical Sciences
Available online 3 April 2019
In Press, Accepted Manuscript

# The EU regulatory landscape of non-biological complex drugs (NBCDs) follow-on products: Observations and recommendations

K. Klein [a, b, c], P. Stolk [a, b, c], M.L. De Bruin [a, d], H.G.M. Leufkens [a, b], D.J.A. Crommelin [e], J.S.B. De Vlieger [b]

Show more

https://doi.org/10.1016/j.ejps.2019.03.029 

85 NBCD-generics approved in the EU.

2 via the centralized procedure EMA
83 outside the centralized procedure.

Examples of clinical non-equivalence described.

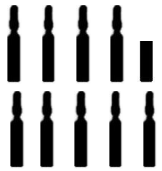
And the US situation?

Next presentations will describe current policies……..

# The switch from Iron Sucrose Similar to Venofer® reduces i.v. iron and EPO dosing in HD-patients[1]

**34.3% less i.v. iron dosing with Venofer ®**

=



960 mg i.v. iron less per HD-patient/year with Venofer® **p<0.001**

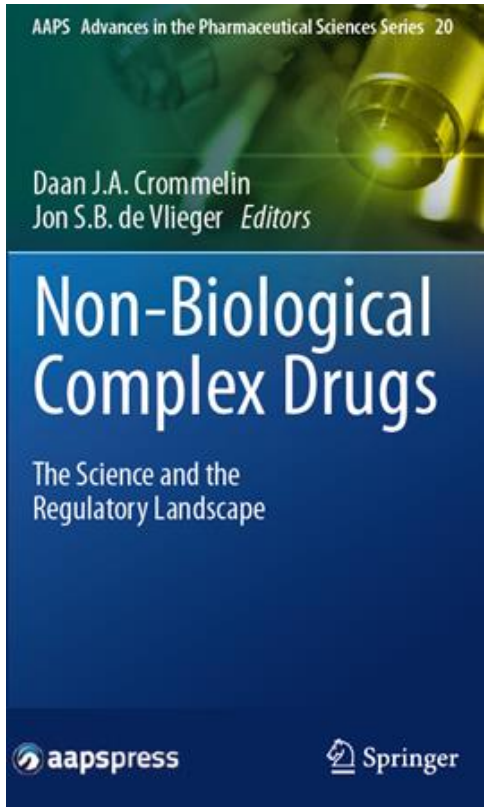
**12.5% less ESA consumption after switching to Venofer®**

=

190.8 µg ESA less per HD-patient/year after switch from ISS to Venofer® **p<0.001**

*1 syringe of epoetin-α calculated as weekly dose of 3'000 IE/0.3 ml (25.2 µg/0.3 ml)

- A prospective, observational multi-centric study comparing two subsequent treatment periods of 13 months each, including 342 HD pats.
- Hb levels were stable over two treatment periods of 13 month each
- $T_{SAT}$ went up from 28.6±7.2% to 30.7±7.6% (**p<0.001**) after switch to Venofer®
- Ferritin increased from 507ng/ml to 579 ng/ml (**p<0.001**) after switch to Venofer®




[1] Agüera ML, PLoS One10(8):e0135967 doi:10.1371/journal.pone.0135967

# Complexity leads to different regulatory approaches


**Doxil**® (USA) marketed as
**Cealyx**® (EU) by Janssen


**Lipodox (Sun Pharma)**

FDA (2012): temporarily imported without approval due to shortage of Doxil

**DOXOrubicin Sun (Sun Pharma)**

FDA (2013): approved as a generic for Doxil

EMA (2016): rejected as a generic for Cealyx


**Copaxone**® Teva Pharmaceuticals


**Glatopa (Momenta)**
FDA: approved in 2015 through Generics application based on sameness defined by FDA, without clinical studies

**Glatiramer Acetate (Synthon)**
EMA: Approved in 2016 through hybrid application, including one Phase III study

# Considerations for Biologics and Non-biological Complex Drugs (NBCDs)

- Introduction: Complex drugs……. A multifaceted landscape
- A glance at the regulatory framework for biosimilars
- CQA assessment, comparability, evolution, drift and divergence
- Formulation: freedom to operate, does it make a/the difference? Stability and handling
- Market penetration in the EU, consequences
- **Non-**Biological Complex Drugs (NBCD): similarity with biosimilars….. Published dissimilarity observed outside the USA. Present regulatory schemes. How to proceed.
- Conclusions

# Conclusions……

The biosimilar concept has gained ground and is affecting the (economy of) the health care system.

The complexity of medicines is increasing at a rapid pace (Nanomedicines and Advanced Therapies Medicinal Products, Combination products) and so are the questions around their quality, handling and affordability.

Are paradigm shifts in the regulatory arena needed?

# Complex Medicines: Science, Regulation, and Accelerating Development


nyas.org/ComplexMedicines2019

#ComplexMedicines2019

May 13, 2019
8:00 AM – 6:00 PM
The New York Academy of Sciences

This symposium will outline the future of complex medicines, including the best scientific approaches for their development and regulation, challenges in the assessment of equivalence, and how to ensure timely access for patients.

**Presented By:**

Non Biological Complex Drugs working group

The New York Academy of Sciences

NCL Nanotechnology Characterization Laboratory