
# Uso de Biossimilares e Genéricos no intercâmbio

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São Paulo, Brasil, 25 Julho 2019

# Declaration

The views and opinions expressed in the following lecture are those of the individual presenter and should not be attributed to University of Lisbon, Infarmed or CEIC (Ethics Committee for Clinical Research).

# The increasing complexity of drugs

***atorvastatin***

Molecular weight

= 558 Daltons

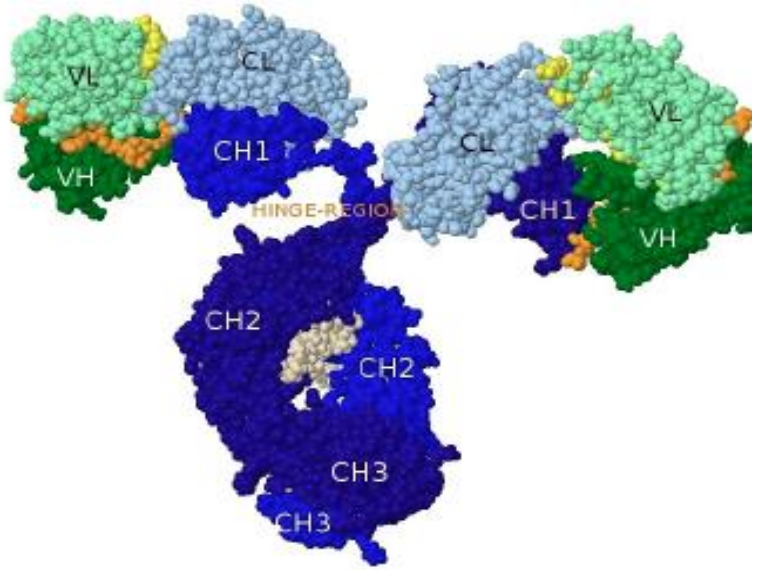
0 amino acids

***Interferon-alpha***

Molecular weight

= 19,625 Daltons

~165 amino acids




***Antibody (IgG)***

Molecular weight

= 150,000 Daltons

~1,300 amino acids

Source: http://www.path.cam.ac.uk/~mrc7/mikeimages.html

# Generics

# MAA - Generic

**Generic Medicinal Product**

DIRECTIVE 2001/83/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 6 November 2001

A medicinal product which has the **same qualitative and quantitative composition in active substances** and the same **pharmaceutical form** as the reference medicinal product, and whose **bioequivalence** with the reference medicinal product has been demonstrated by appropriate bioavailability studies.

# MAA - Generic

- The medicinal product is a generic of a reference medicinal product which is or has been authorised under Article 6 for not less than **eight years** in a Member State or in the Community.

- Same qualitative and quantitative **composition** in active substances as the reference medicinal product

- same **pharmaceutical form** as the reference medicinal product. The various immediate-release oral pharmaceutical forms shall be considered to be one and the same pharmaceutical form (*Standard Terms*);

- **Bioequivalence** with the reference medicinal product has been demonstrated by appropriate bioavailability studies (possibility of waiver if fulfilled the specific criteria in the relevant guidelines e.g. Guideline on The Investigation of Bioequivalence);

# MAA - Generic

- **Documentation:**

  Module 1

  Module 2

  Results and report of

  – Quality (Module 3)

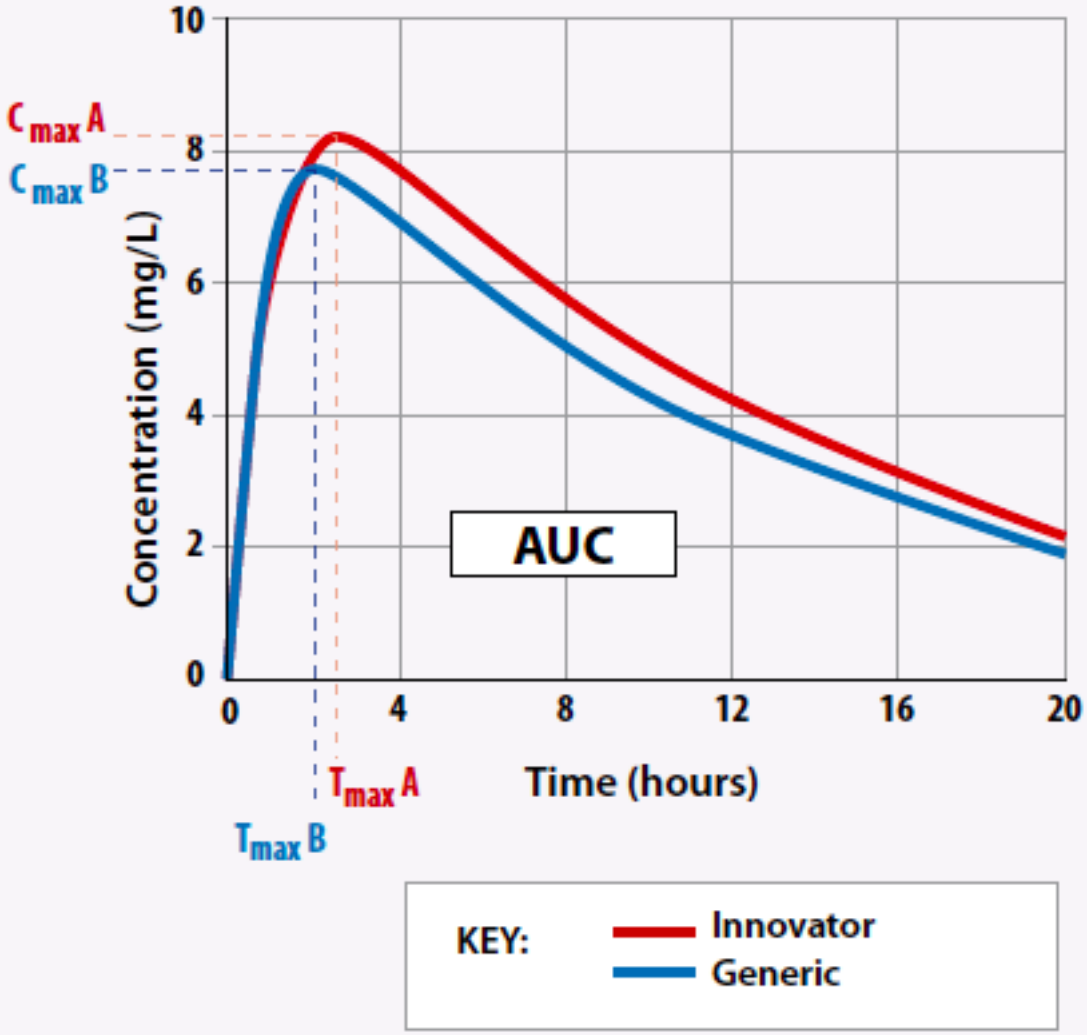
  – Clinical (Module 5) } Bioequivalence study

# Bioavailability

Bioavailability is a measurement of the extent of a therapeutically active medicine that reaches the systemic circulation and is therefore available at the site of action.

In order to determine that two medicines are bioequivalent there must be no more than a 20% difference between the AUC and Cmax.
This is based on international consensus that differences less than this are not clinically significant. In order to establish this, the AUC and Cmax for the generic medicine are compared to that for the innovator medicine

# Bioequivalence



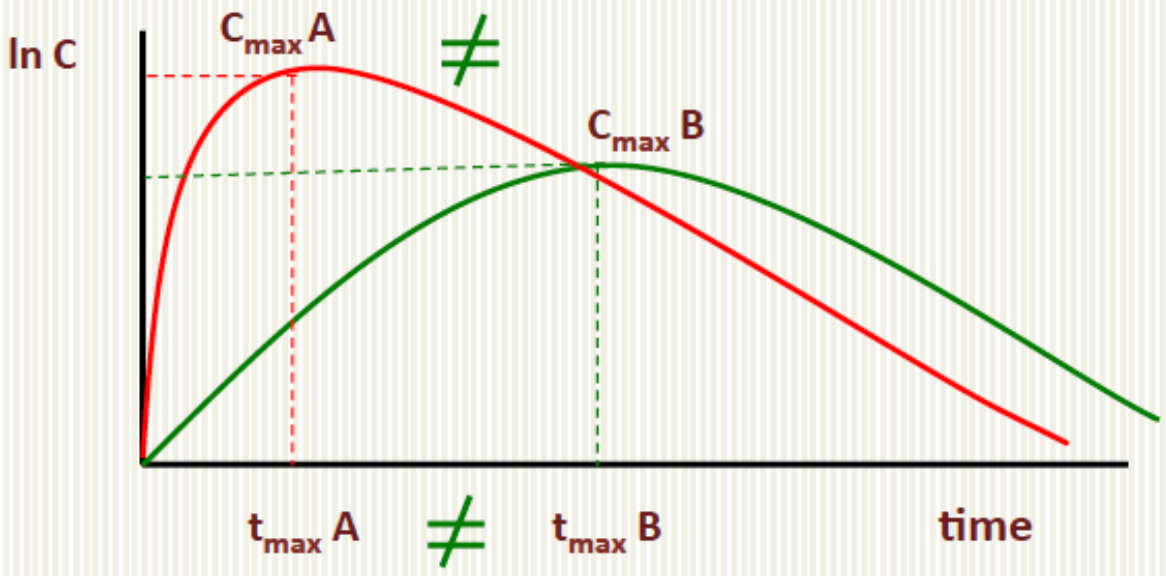

$C_{max}$ maximum plasma drug concentration

$T_{max}$ time required to achieve a maximal concentration

**AUC** total area under the plasma drug concentration-time curve

# Bioequivalence

Extent *and* rate of absorption




These products are not bioequivalent !

De: R. Lobato

# Bioequivalence

## Standard design

- randomised, two-period, two-sequence, single dose crossover study
- washout between periods (≥ 5 t½)
- healthy volunteers, both genders (unless unethical)
- two treatments (*test* and *reference*)
- multiple dose study (at *steady state*) if:
  - problems of sensitivity of the analytical method (exceptionally)
  - patients population
  - modified release products

# Statistical analysis

**Maximum difference between products: 20%**

80/100 = 0.80 100/80 = 1.25

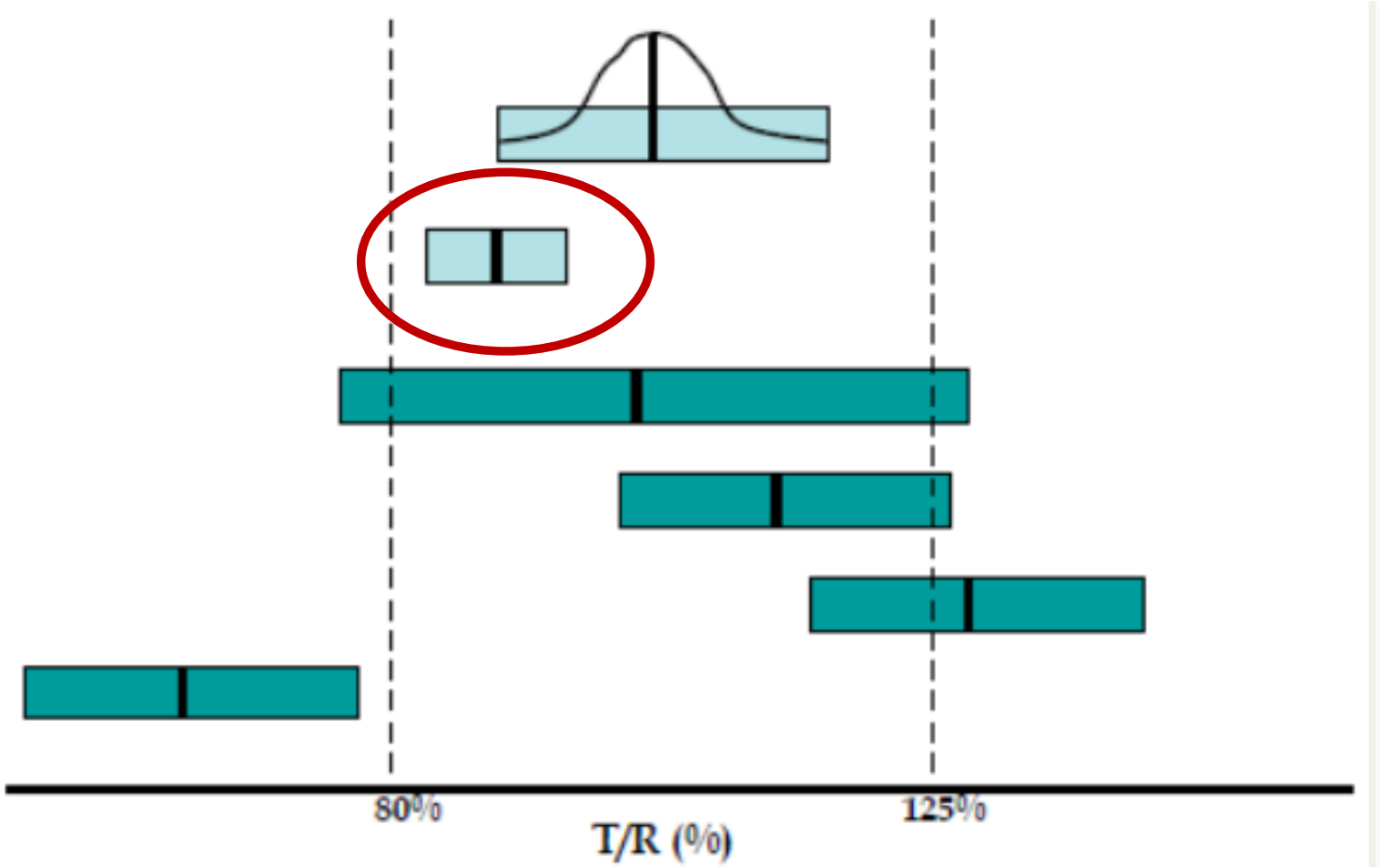
**Acceptance limits**

**AUC e Cmax (test/ref): 80.00 < Test/Ref < 125.00**

***In very special circumstances, acceptance interval may be tightened or widened.***

**$t_{max}$: statistical evaluation is not required.**

# Statistical analysis



# Generic medicine
# Bioequivalence

European Medicines Agency

London, 20 January 2010
Doc. Ref.: CPMP/QWP/EWP/1401/98 Rev. 1

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE
(CHMP)

GUIDELINE ON THE INVESTIGATION OF BIOEQUIVALENCE

| | |
|---|---|
| DISCUSSION IN THE JOINT EFFICACY AND QUALITY WORKING GROUP | December 1997 – October 1998 |
| TRANSMISSION TO CPMP | July 1998 |
| RELEASE FOR CONSULTATION | December 1998 |
| DEADLINE FOR COMMENTS | June 1999 |
| DISCUSSION IN THE DRAFTING GROUP | February – May 2000 |
| TRANSMISSION TO CPMP | July – December 2000 |
| RELEASE FOR CONSULTATION | December 2000 |
| DEADLINE FOR COMMENTS | March 2001 |
| DISCUSSION IN THE DRAFTING GROUP | March - May 2001 |
| TRANSMISSION TO CPMP | July 2001 |
| ADOPTION BY CPMP | July 2001 |
| DATE FOR COMING INTO OPERATION | January 2002 |
| DISCUSSION ON REV. 1 IN THE PK-GROUP OF THE EFFICACY WORKING PARTY | May 2007-July 2008 |
| DISCUSSION ON REV. 1 BY THE QUALITY WORKING PARTY | June 2008 |
| DRAFT REV. 1 AGREED BY THE EFFICACY WORKING PARTY | 8 July 2008 |
| ADOPTION REV. 1 BY CHMP FOR RELEASE FOR CONSULTATION | 24 July 2008 |
| END OF CONSULTATION REV. 1 (DEADLINE FOR COMMENTS) | 31 January 2009 |

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***Guideline on the Investigation of Bioequivalence***

***CPMP/EWP/QWP/1401/98***

***Rev. 1, Janeiro 2010***

# Quality of generic medicines?

# Quality of Medicines - Market Monitoring Analyzed products(2004-2012)

| Tipo de Amostra | Nº MED analisados | Nº NC | Nº Recolhas de Lote | (%) Recolhas de Lote |
|---|---|---|---|---|
| Medicamentos Genéricos | 1405 | 103 | 26 | 1,9% |
| Medicamentos Não Genéricos | 1761 | 173 | 40 | 2,2% |
| Total | 3166 | 276 | 66 | 2,1% |

# Biosimilars

# Biologics and Biosimilars

- Biological medicine

A medicine whose active substance is made by a living organism.

- Biosimilar medicine

A biosimilar is a biological medicine highly similar to another biological medicine already approved in the EU (called 'reference medicine') in terms of structure, biological activity and efficacy, safety and immunogenicity profile (the intrinsic ability of proteins and other biological medicines to cause an immune response)

# Biosimilars

A biosimilar is a biological medicine **highly similar** to another biological medicine already approved in the EU (called ‘reference medicine’) in terms of structure, biological activity and efficacy, safety and immunogenicity profile (the intrinsic ability of proteins and other biological medicines to cause an immune response).

# Biosimilar Medicinal Product

- biological medicinal product containing a version of the active substance of an already authorised original biological medicinal product (reference medicinal product).

- has to demonstrate similarity to the reference medicinal product in terms of quality characteristics, biological activity, safety and efficacy based on a comprehensive comparability exercise.

# Generics vs Biosimilars

| | Generics | Biosimilars |
|---|---|---|
| **Particulars** | Simple<br>Small<br>Stable | Complex<br>Large<br>Less stable |
| **Characterization** | Easy to characterize | Difficult to characterize |
| **Manufacturing process** | Chemical process<br>Easy to reproduce<br>Identical copies | Biological substances<br>Biological processes<br>Extremely complex:<br>Difficult to reproduce<br>Similar copies<br>The 'process' is the 'product' |
| **Abbreviated MA procedure** | Bioequivalence | Comparability studies<br>to demonstrate similarity |

**Biosimilars are NOT generics!**

# European Guidelines

2005

EMA published a guideline, being the first agency worldwide to develop specific regulations in this area: "*Guideline on similar medicinal biologic products*" - *CHMP/437/04*".

Requires that, relative to a comparator (reference product), the applicant demonstrates physical, chemical and biological comparability.

This requires an extensive analysis of the two drugs, with advanced techniques. It is fundamental to confirm the chemical and physical comparability of both medicines.

# European Guidelines

## 2013

EMA updates the guideline with the same the main.

Describes and analyzes the application of "biosimilar" approach, the choice of reference biotech and principles to establish biosimilarity.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

23 October 2014
CHMP/437/04 Rev 1
Committee for Medicinal Products for Human Use (CHMP)

Guideline on similar biological medicinal products

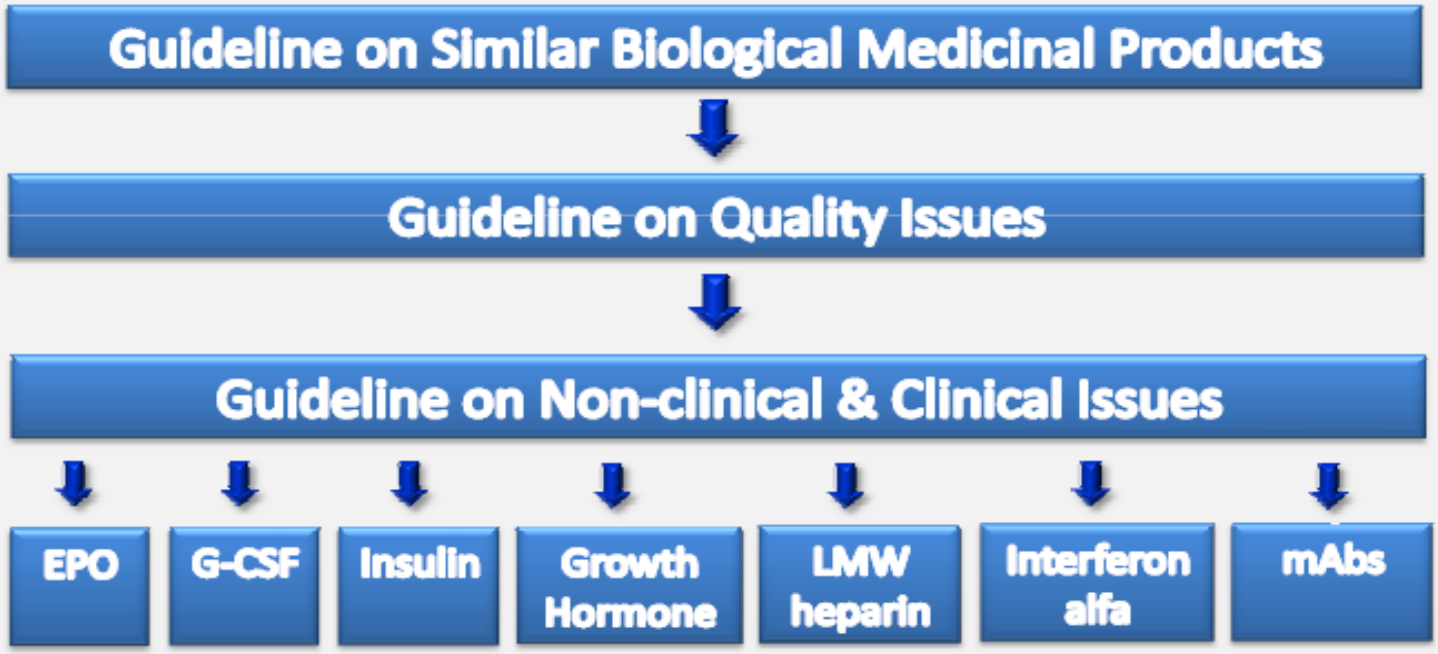
| | |
|---|---|
| Draft agreed by Biosimilar Medicinal Products Working Party and Biologics Working Party | March 2013 |
| Adopted by CHMP for release for consultation | 25 April 2013 |
| Start of public consultation | 30 April 2013 |
| End of consultation (deadline for comments) | 31 October 2013 |
| Revised draft agreed by Biosimilar Medicinal Products Working Party and Biologics Working Party | July 2014 |
| Adoption by CHMP | 23 October 2014 |
| Date for coming into effect | 30 April 2015* |

* After adoption by CHMP applicants may apply some or all provisions of this guideline in advance of this date.

This guideline replaces the Guideline on similar biological medicinal products (CHMP/437/04).

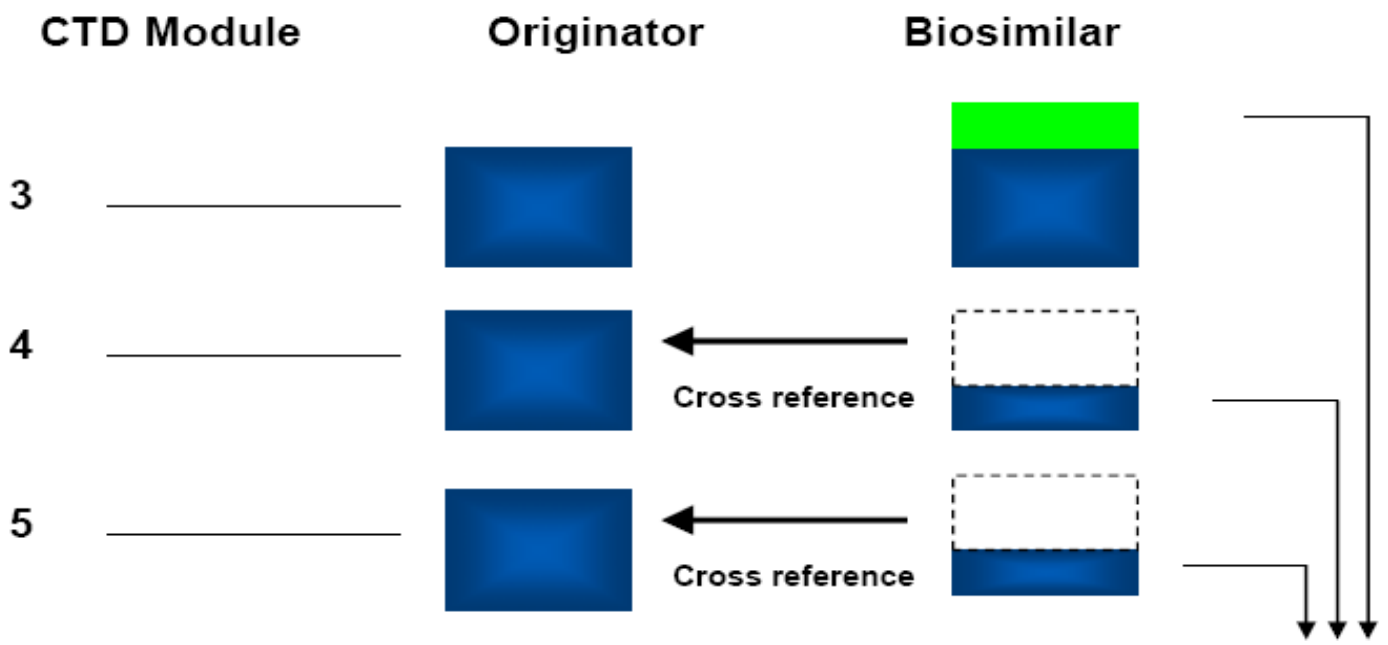
# European Guidelines

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

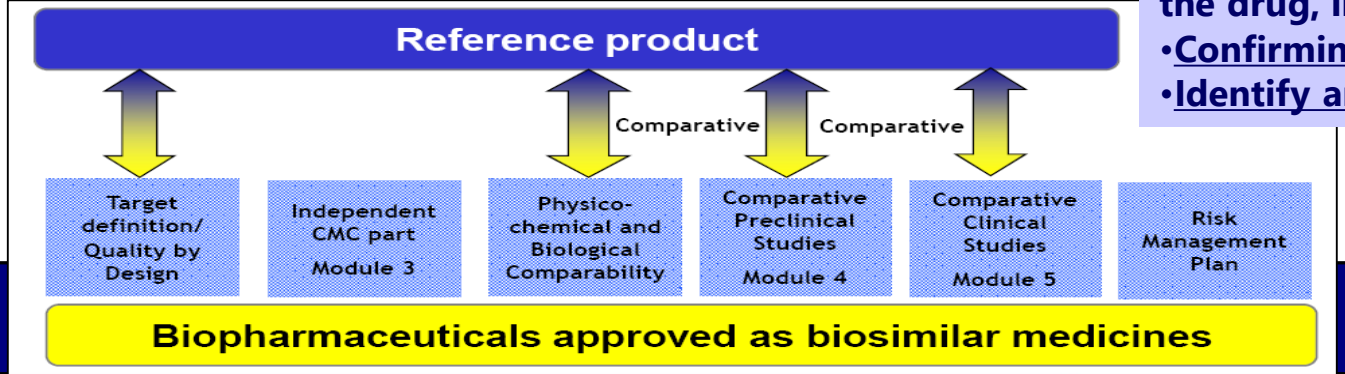



Overview of biosimilar guidelines developed by EMA (since 2006)

# Comparability




Cross reference – class specific Safety and Efficacy




**COMPARATIVE studies with Reference**

**"Integrated Exercise Comparability", specific to the drug, in aspects of Q, S and E for:**

- **Confirming the similarities, differences**
- **Identify and evaluate the impact**

# Comparability

- Quality
  - physico-chemical characterization (molecular structure)
  - biological characterization (functionality)
- Non clinical studies
  - in vitro studies (receptors binding, cells assays )
  - In vivo studies (PD effect, nonclinical toxicity)
- Clinical studies
  - Pharmacokinetics (PK)
  - Pharmacodynamics (PD)
  - Clinical trials on efficacy and safety
  - [Combined trials PK / PD]

**Any difference on S or E profile between the reference product and biosimilar must be justified**

# Biosimilarity

- Bio-similar

- can NOT be:
  - Bio-worse
  - Bio-better

# Indications extrapolation

In case the originally authorized medicinal product has more than one indication, the efficacy and safety of biosimilar has to be justified or demonstrated separately for each of the therapeutic indications.

At least one comparative trial (efficacy and safety) in a "sensitive" population with relevant clinical endpoints

It is possible the extrapolation to other indications of the reference product, (not studied during the development of biosimilar) based on the overall evidence of comparability.

The acceptance of indications extrapolation is decided on a case-by-case basis, depending on the strength of scientific demonstration of comparability

# Immunogenicity

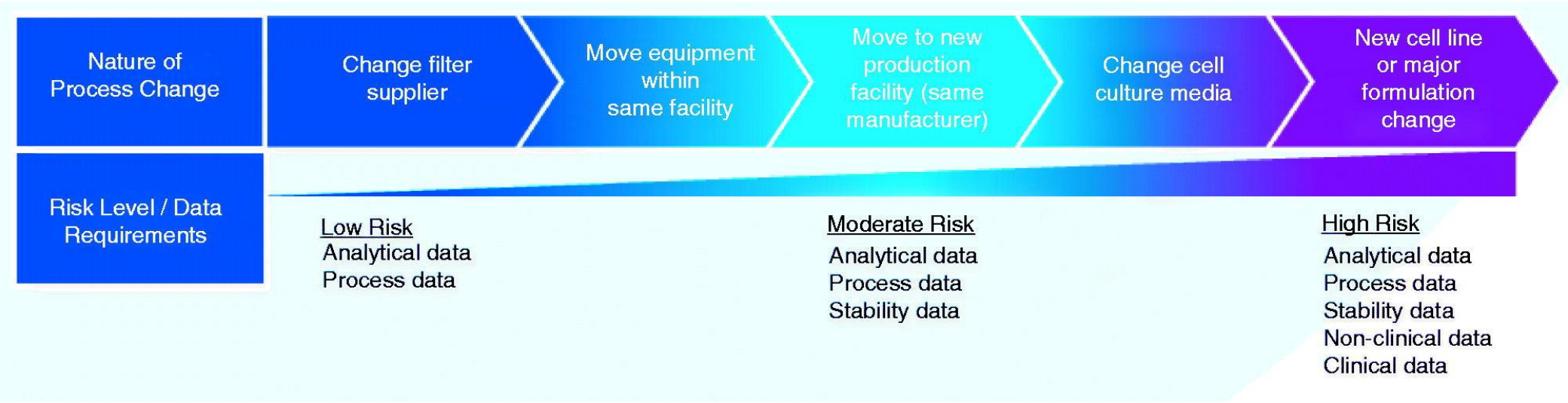
Patient can develop antibodies against a therapeutic protein (minimization of the therapeutic effect and / or anaphylactic reactions).

Immunogenic potential of a specific biological drug in each patient is almost unpredictable. Replacement, particularly in a patient whose condition is controlled and stabilized, with a similar biological medicinal product must be carefully considered.

The biological drugs or their biosimilars can have different manufacturing conditions and composition, and this may confer different immunogenic potential.

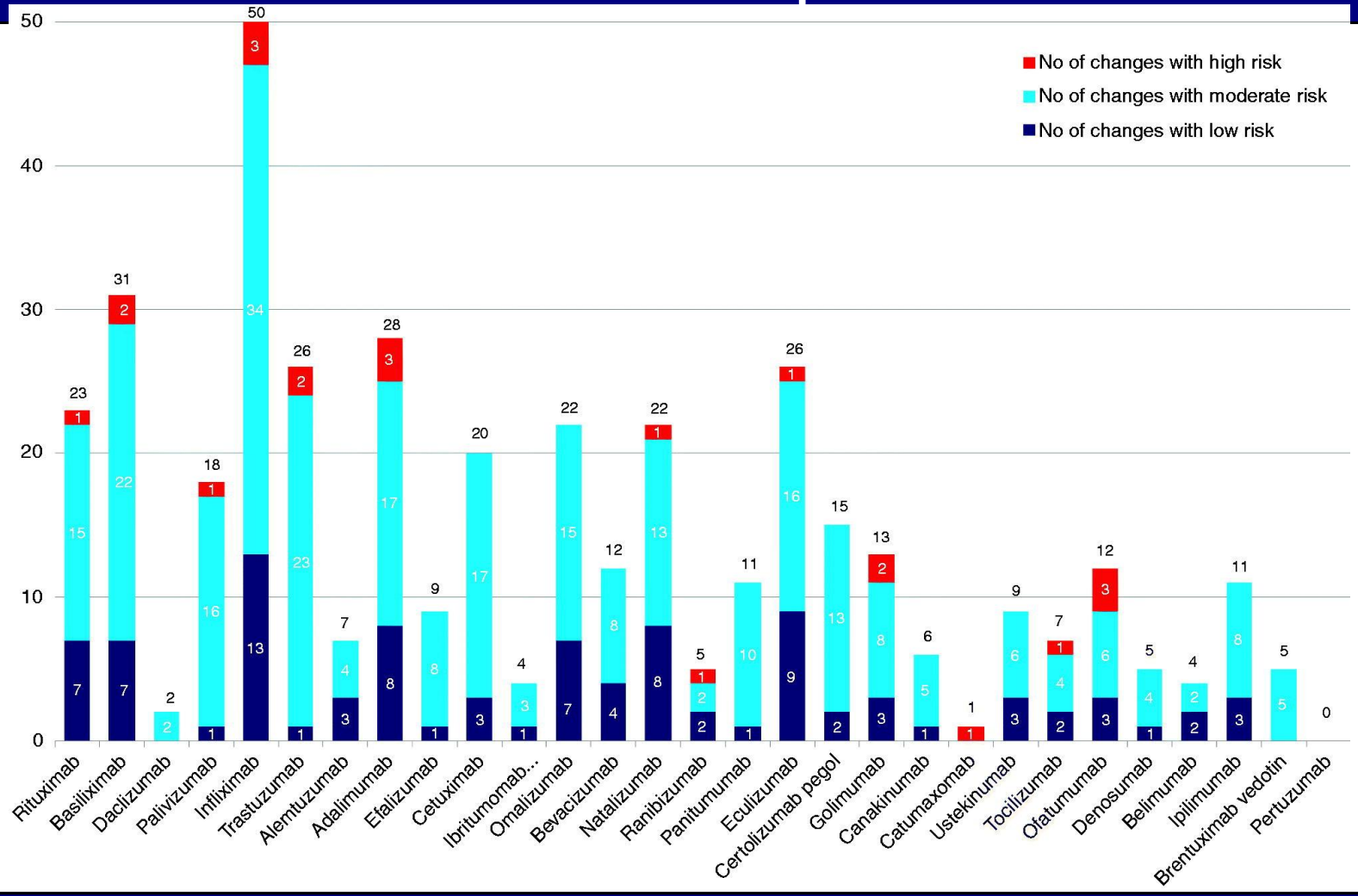
Unpredictability of the immunogenic potential applies to the substitution of a reference medicinal product for a biosimilar or vice versa, but also between different manufacturing changes during the lifecycle of a medicinal product .

# Manufacturing changes for biotechnology products were categorized as low/moderate/high risk




Vezer et al., Curr Med Res Opin 2016;32:829–34

# Number of manufacturing changes for mab (reference products)




Vezer et al.,
Curr Med Res Opin 2016;32:829–34

# RTC and new drug development paradigm

- HCP have been trained with the principles of "evidence based" medicine, with the controlled clinical trial as a standard.
- Biosmilars are built on a new drug development paradigm
- Emphasis is on laboratory and pre-clinical work
  - Is based on a similarity exercise
  - The clinical trial is to support similarity, NOT to proof efficacy

Is understandable that physicians are reluctant to prescribe these drug

# Science, not Emotions

# Biosimilars in Europe…

- The EU has **pioneered the regulation** of biosimilar medicines by establishing a **solid framework** for their approval and by shaping biosimilar development globally.

- The evidence acquired over more than 10 years of clinical experience shows that biosimilars approved through EMA can be used as **safely and effectively in all their approved indications** as other biological medicines.

# In Europe:

*"I don't trust in biosimilars"*

is similar to

*"I don't trust in regulatory authorities"*

...and the same applies to generics!

# Misunderstandings HCP may have about biosimilars

- May be of less quality as the innovator drug
- Are poorly supported by research
- Have not been researched in all indications
- Differ from the innovator in potentially relevant aspects
- Have been assessed by regulators who are bureaucrats, who have no clinical experience
- Used a shortcut in the normally rigorous licensing process

# How to build trust in biosimilars?

**Reduce the information gap**

**Avoid trouble around switching**

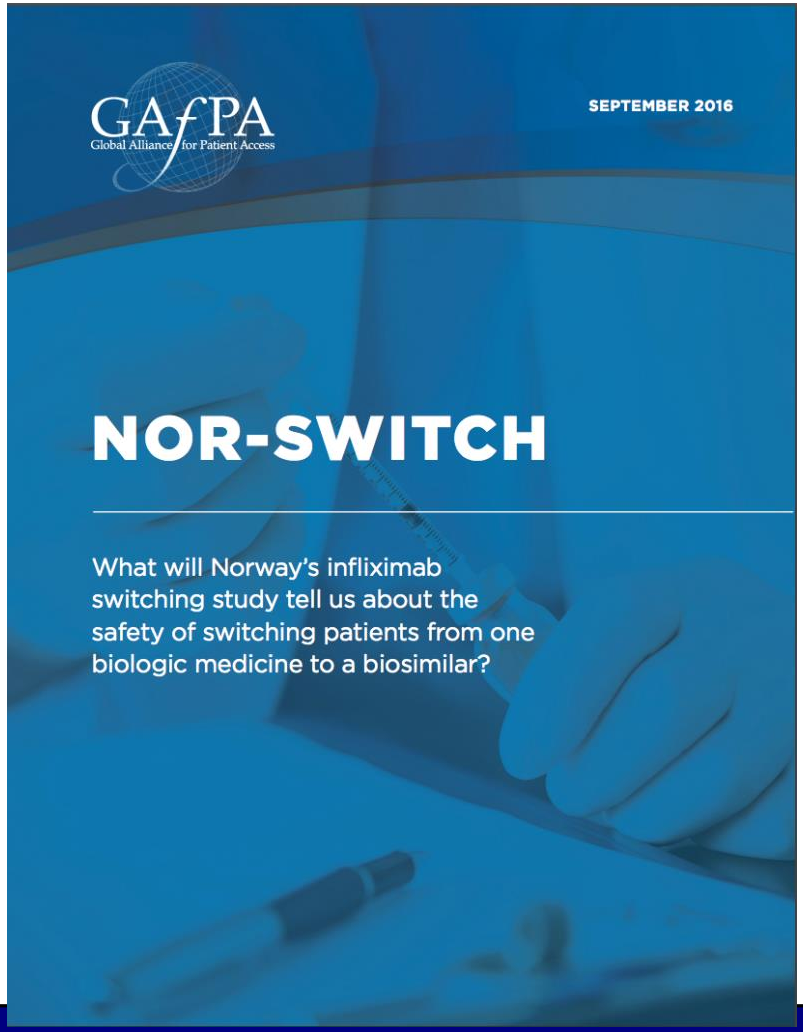
# Interchangeability

Any biological / biosimilar, is likely to be used for an approved therapeutic indication.

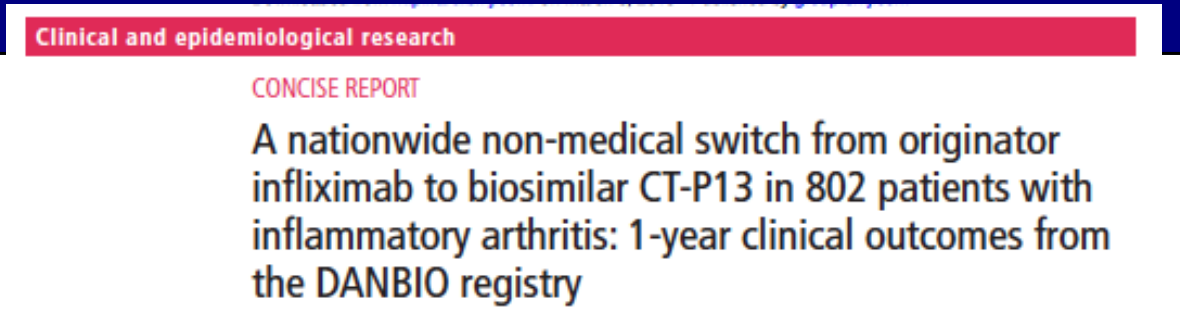
Many of the potential differences do not result in any clinically-significant risk, however, any change should ensure stability cycles using the same drug for long periods of time and always guarantee a correct and rigorous pharmacovigilance risk management plan.

Situations where there is a change in treatment with biological drugs (replacement by another biologic drug or significant changes during the life cycle of the same biological medicine) requires medical monitoring.

# NOR-SWITCH study



# DANBIO


Clinical and epidemiological research

CONCISE REPORT

A nationwide non-medical switch from originator infliximab to biosimilar CT-P13 in 802 patients with inflammatory arthritis: 1-year clinical outcomes from the DANBIO registry

- **CONCLUSION:**

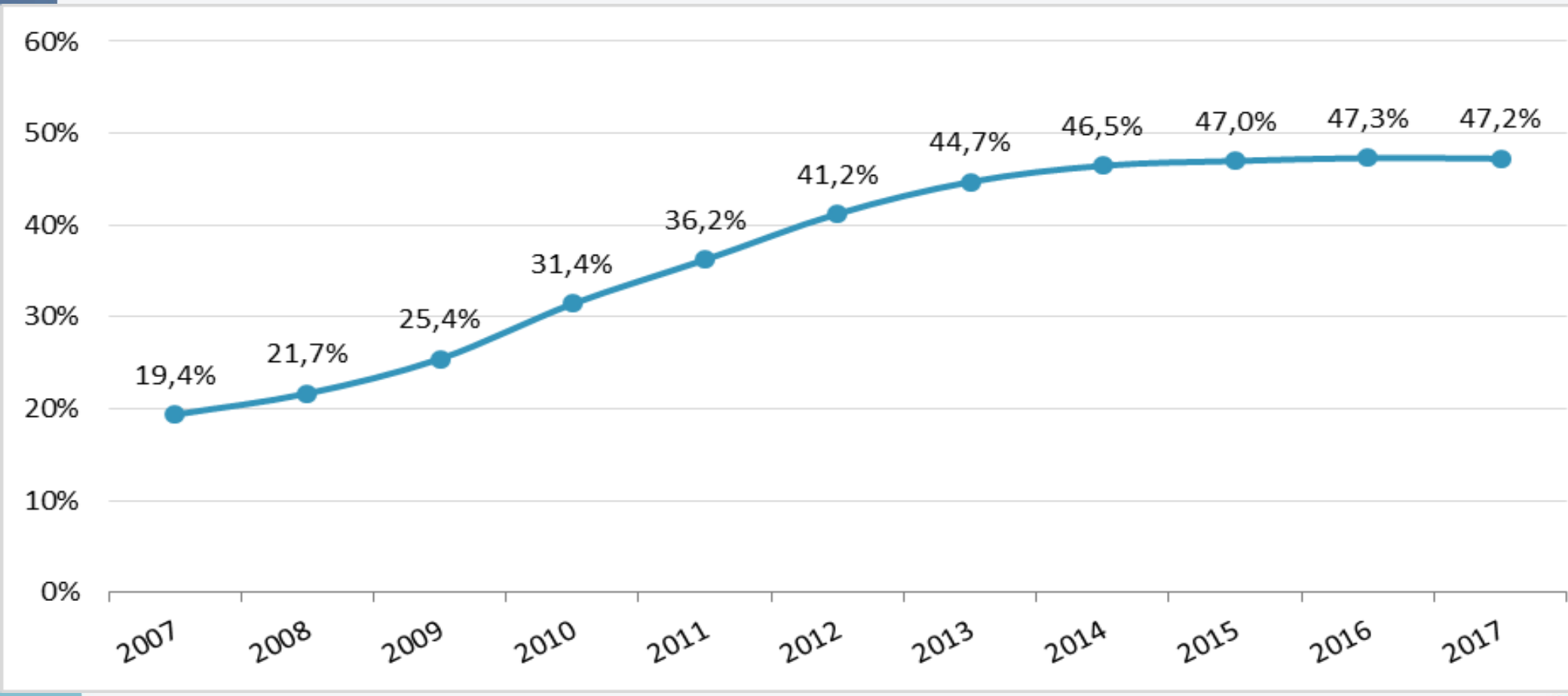
In 802 arthritis patients treated with INX for median >6 years, a nationwide non-medical switch to CT-P13 had no negative impact on disease activity. Adjusted 1-year CT-P13 retention rate was slightly lower than for INX in a historic cohort.

Glintborg B, *et al*. *Ann Rheum Dis* 2017;**76**:1426–1431.

# Role of generics and biosimilars on the increase of access and sustainability of health systems

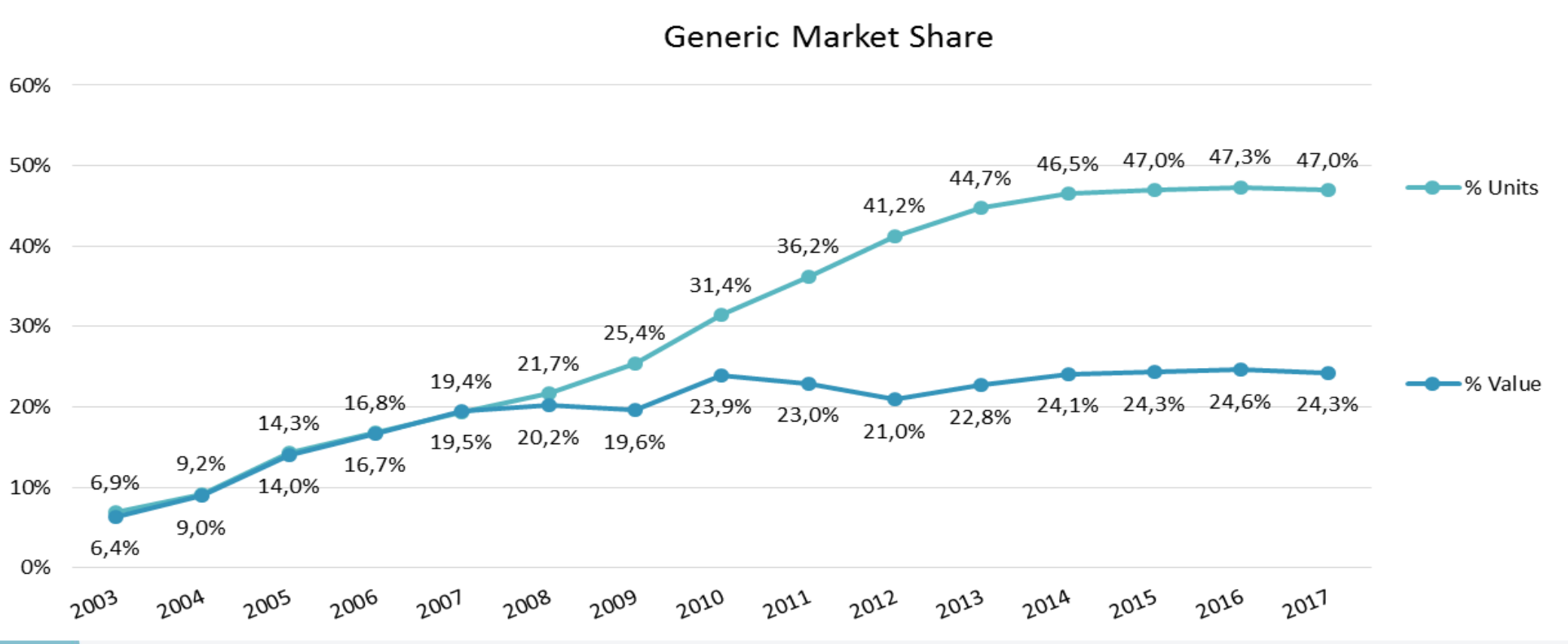
# Generics Market Share Portugal

**Ambulatory market**



# Generics Market Share Portugal

Generics market share evolution (until march 2017)



# Biologics

| Top Expenditure (Portuguese NHS) | 2016 |
|---|---|
| Emtricitabine + Tenofovir | 56 M€ |
| **Adalimumab** | **38 M€** |
| Darunavir | 31 M€ |
| **Trastuzumab** | **31 M€** |
| Abacavir + Lamivudine | 28 M€ |
| **Imatinib** | **28 M€** |
| **Etanercept** | **27 M€** |
| **Human Normal Immunoglobulin** | **23 M€** |
| Raltegravir | 22 M€ |
| **Infliximab** | **21 M€** |

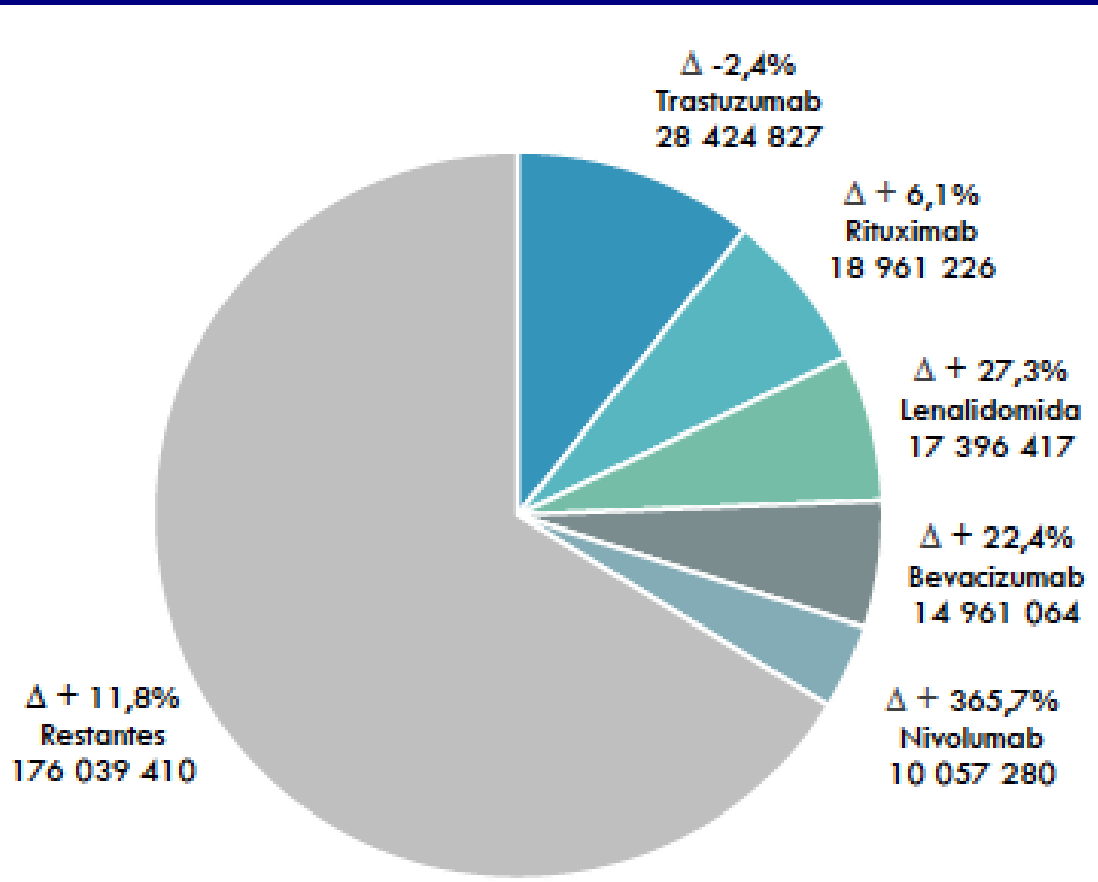
# Biologics

| Top Expenditure (Portuguese NHS) | Jan-Nov 2017 |
|---|---|
| Emtricitabine + Tenofovir | 45 M€ |
| **Adalimumab** | **34 M€** |
| **Trastuzumab** | **28 M€** |
| Darunavir | 28 M€ |
| **Human Normal Immunoglobulin** | **27 M€** |
| **Etanercept** | **24 M€** |
| Emtricitabine + Rilpivirine + Tenofovir | 24 M€ |
| Raltegravir | 21 M€ |
| **Infliximab** | **20 M€** |
| **Rituximab** | **19 M€** |

# Oncology

24.8% of total expenditure

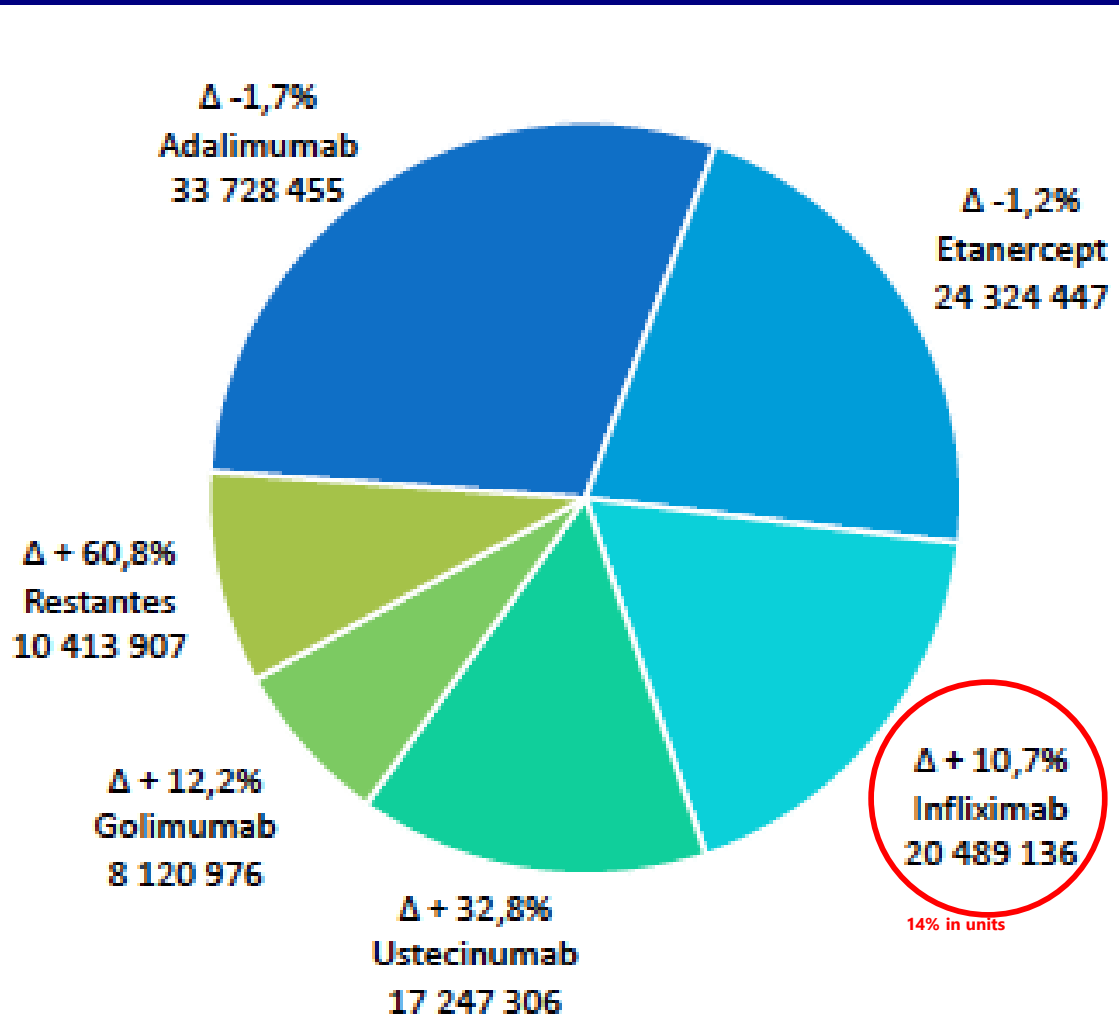
266 M€ (Δ +14%)



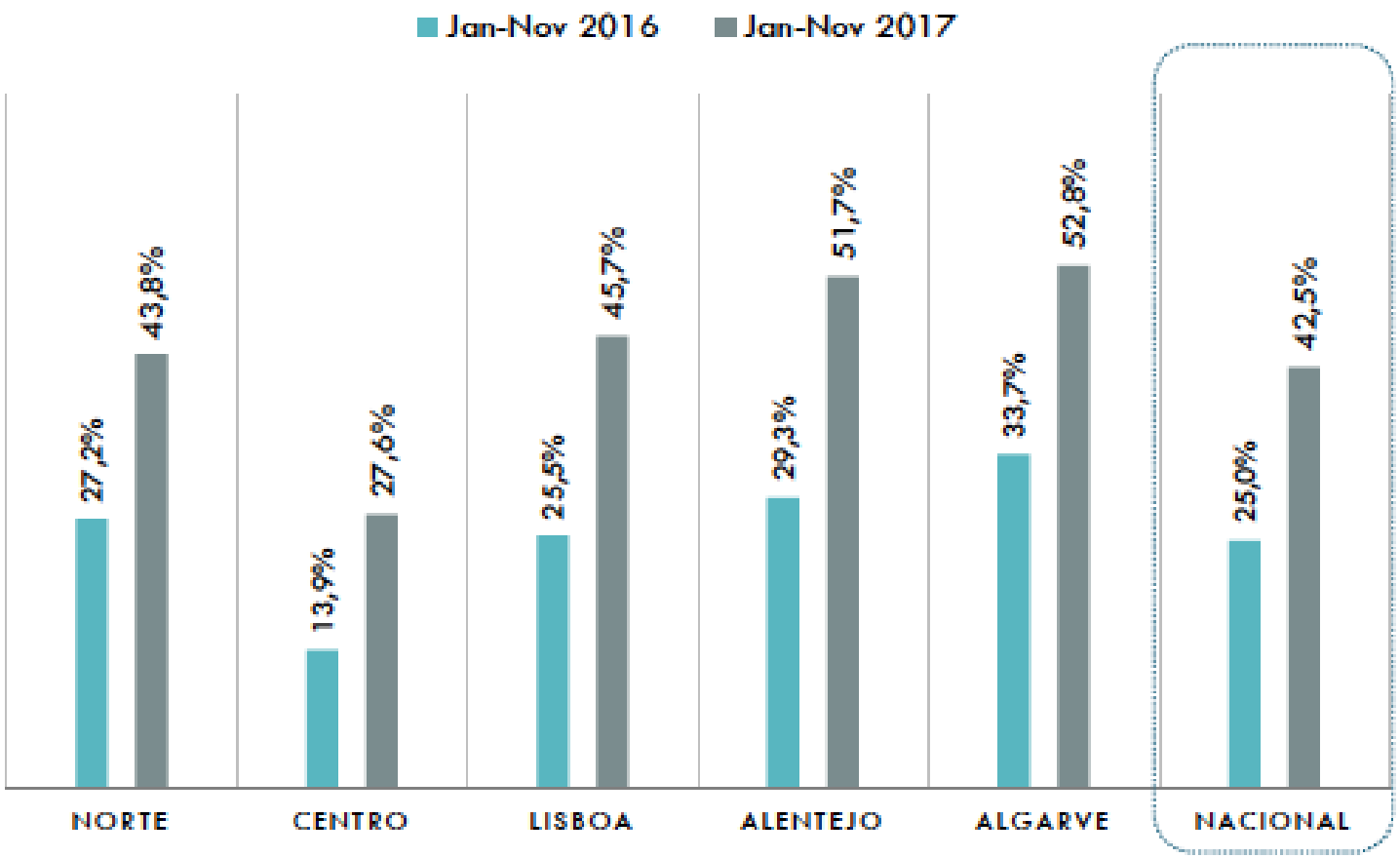
# Rheumatoid arthritis and Psoriasis

10.7 % of total expenditure

114 M€ (Δ +9.8%)



# Infliximab




January-November 2017

National share: 42.5%

# What Biosimilars are Approved and When?

| | |
|---|---|
| 2006 | Somatropin |
| 2007 | Epoetin alfa, Epoetin zeta |
| 2008 | Filgrastim |
| 2013 | Infliximab, Follitropin alfa |
| 2014 | Insulin glargine |
| 2016 | Etanercept, Enoxiparin sodium |
| 2017 | Rituximab, Adalimumab, Insulin lispro, Teriparatide |
| 2018 | Bevacizumab |

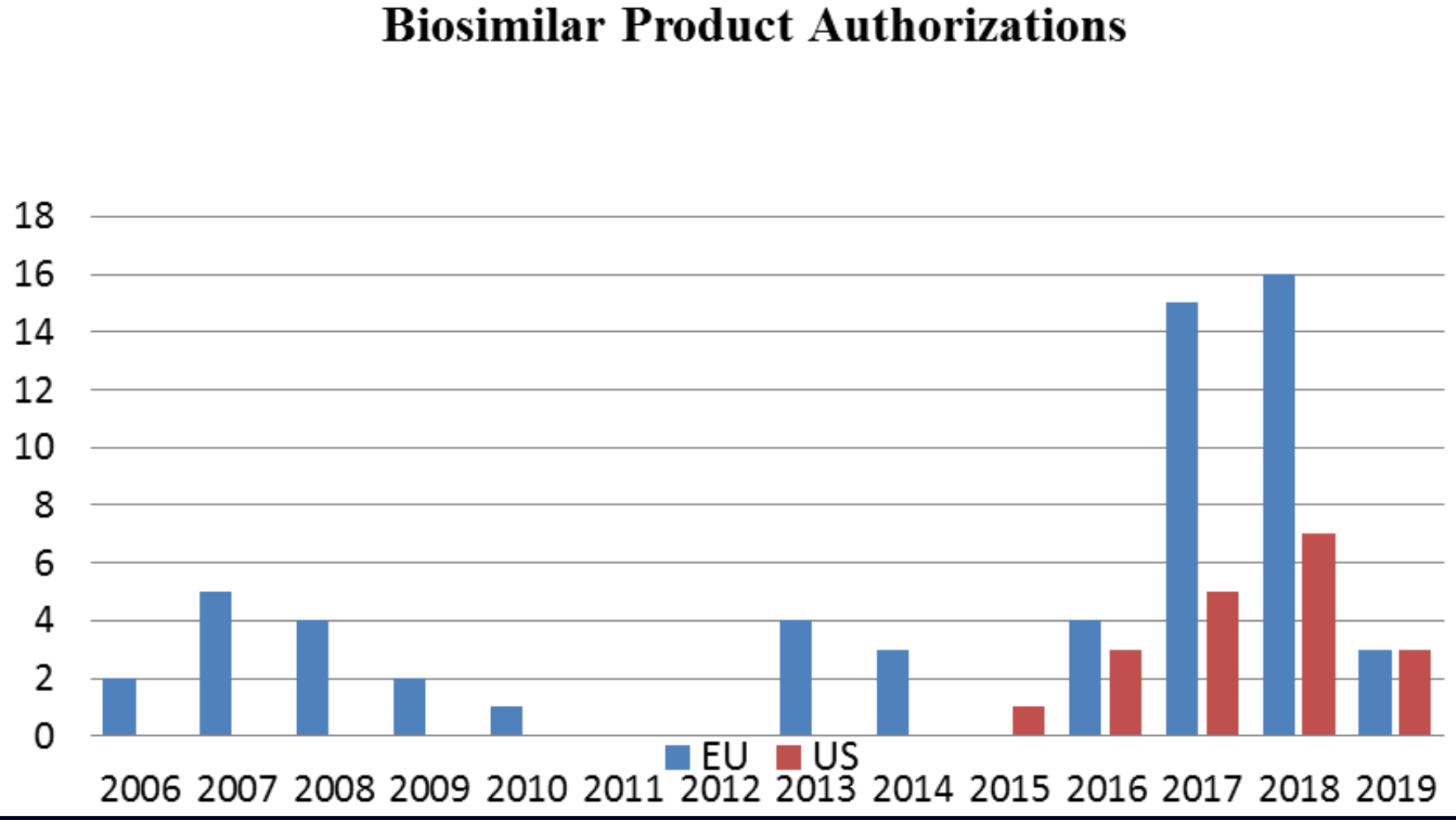
# Biosimilars applications under review by EMA – January 2019

**Table 1: Biosimilars under review by EMA***

| Common name | Therapeutic area | Number of applications | EMA-approved originator(s) | Originator company(ies) |
|---|---|---|---|---|
| Adalimumab | Immunosuppressant | 3 | Humira | AbbVie |
| Etanercept | Immunosuppressant | 1 | Enbrel | Amgen/Pfizer |
| Pegfilgrastim | Immunostimulant | 1 | Neulasta | Amgen |
| Rituximab | Antineoplastic medicine (anticancer) | 2 | MabThera/Rituxan | Roche |
| Total | | 7 | | |

*Data collected on 25 January 2019.
Source: EMA

# EU vs US


Biosimilar Product Authorizations
18
16
14
12
10
8
6
4
2
0
EU
US
2006
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018
2019

# Challenge?

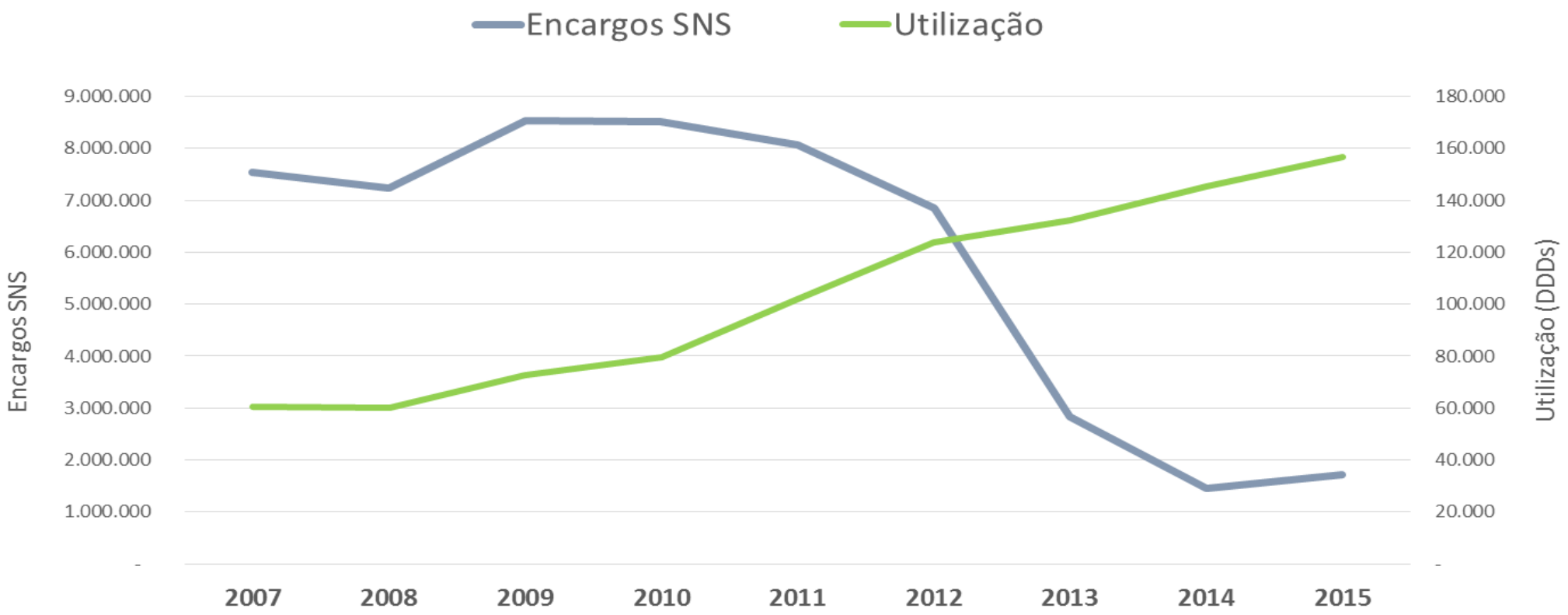
Biosimilars can contribute:

For a safe and better use of existing resources, contributing for the sustainability of health systems.

To give access of biologics to a growing number of patients with therapeutic indication.

# Biosimilars Medicines

## Filgrastim Example



# Obrigado!

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