Sistema Socio Sanitario
Regione Lombardia
ASST Pavia

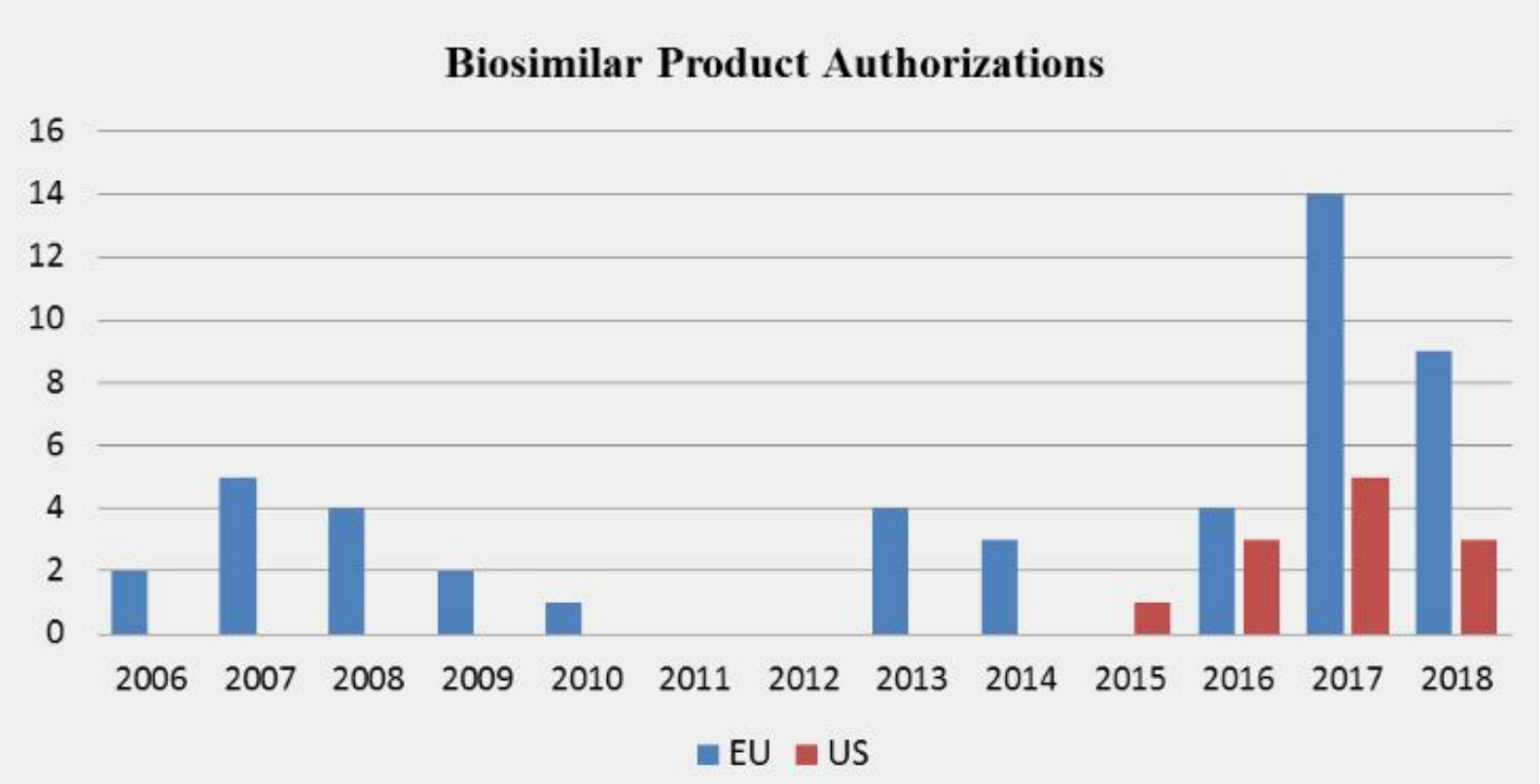
anticoagulanti biosimilari

N.L. Liberato

F.C.S.A.
Federazione Centri per la diagnosi della trombosi e la Sorveglianza delle terapie Antitrombotiche (FCSA)

XXIX Congresso Nazionale FCSA

Bologna,22-23 Ottobre 2018


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

BIOSIMILARE

medicinale simile per qualità, efficacia e sicurezza al prodotto biologico originatore di riferimento non più soggetto a copertura brevettuale

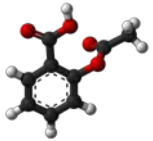
BIOLOGICO

medicinale che contiene una o più sostanze attive derivate da una fonte biologica o ottenute attraverso un processo biologico, e che necessita di una rigorosa standardizzazione delle fasi di produzione e di controlli chimico-fisici e biologici integrati

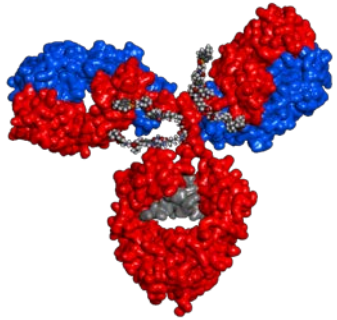
BIOSIMILAR DRUGS ARE NOT GENERICS

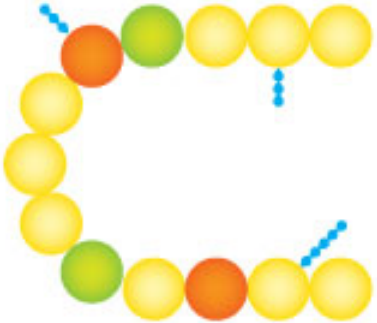
Farhad Zangeneh, MD[1]; Richard Dolinar, MD[2,3]

ENDOCRINE PRACTICE Vol 22 No. 1 January 2016

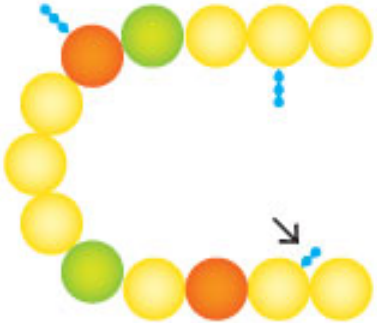


CHEMICAL	BIOLOGICAL
produced by chemical synthesis	**produced by cell cultures**
low molecular weight	high molecular weight
well-defined structure	complex, heterogeneous structure
mostly process-independent	strongly process-dependent
completely characterized	impossible to fully characterize the molecular composition and heterogeneity
stable	unstable
mostly non-immunogenic	immunogenic





Batch 1



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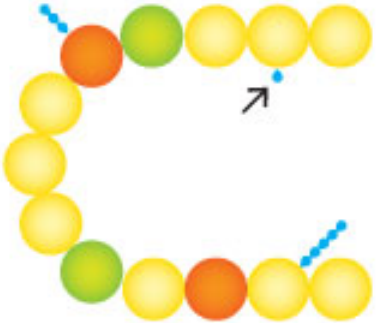

Batch 3

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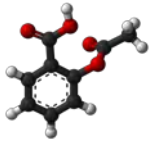

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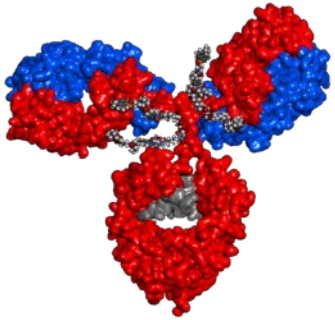

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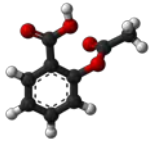

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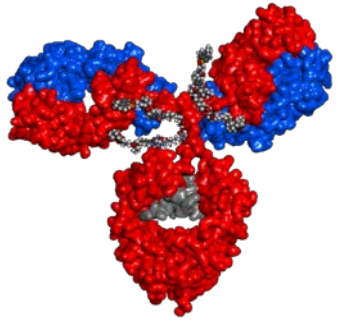

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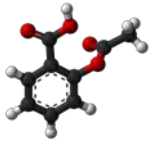

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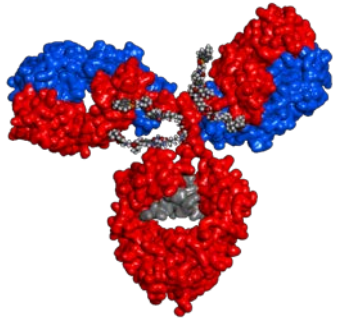

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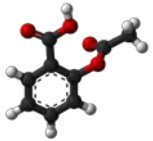

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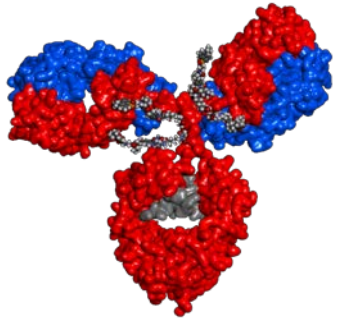

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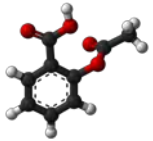

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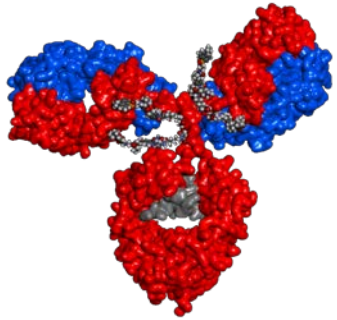

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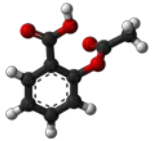

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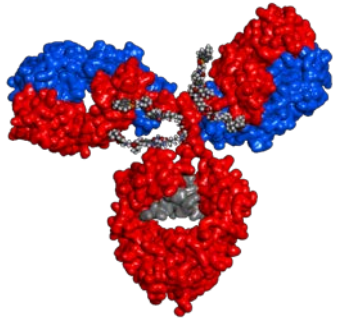
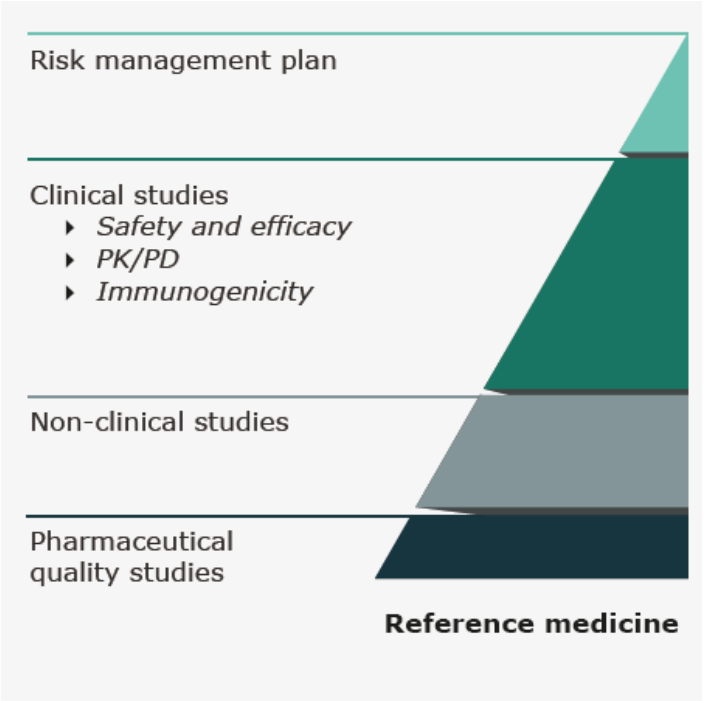
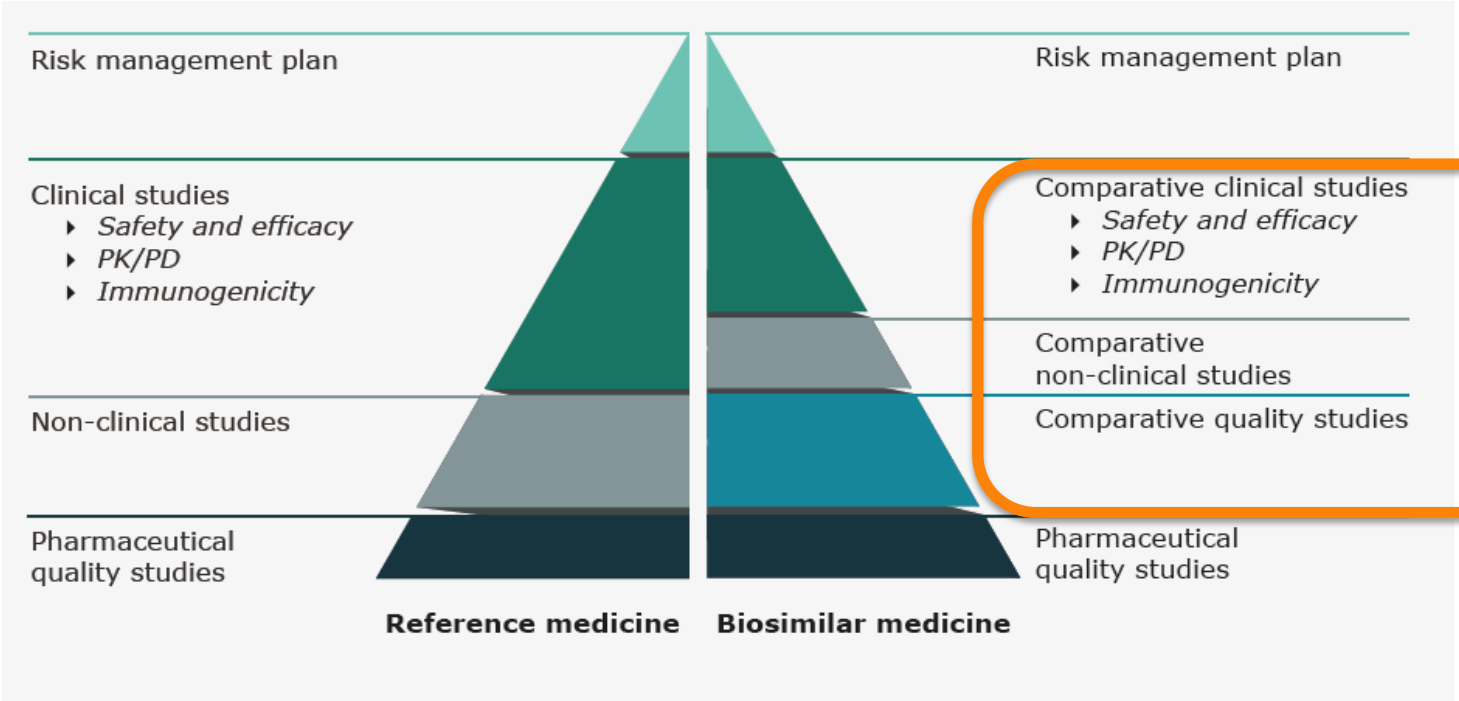
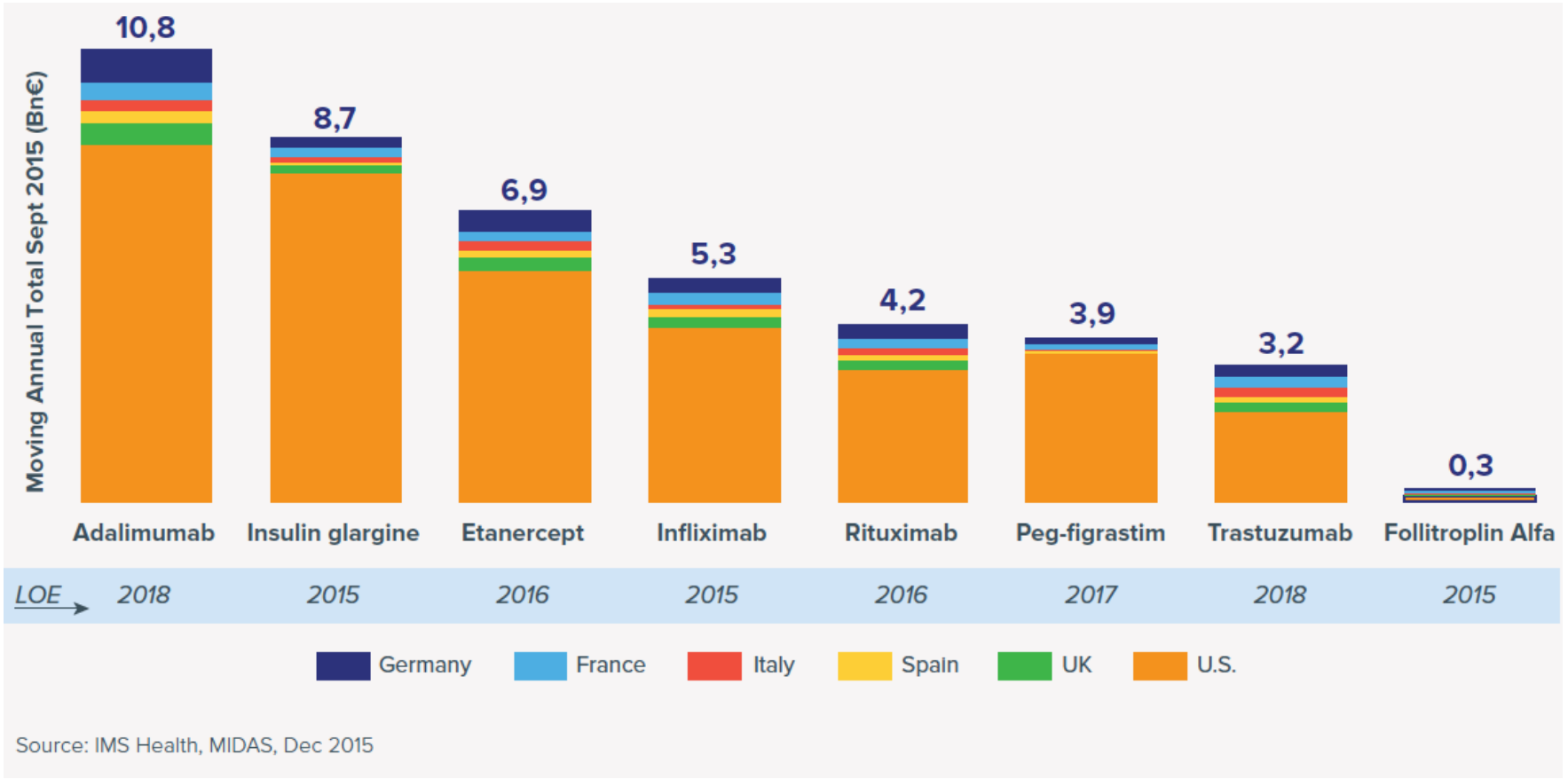



Risk management plan
Clinical studies
Safety and efficacy
PK/PD
Immunogenicity
Non-clinical studies
Pharmaceutical quality studies
Reference medicine

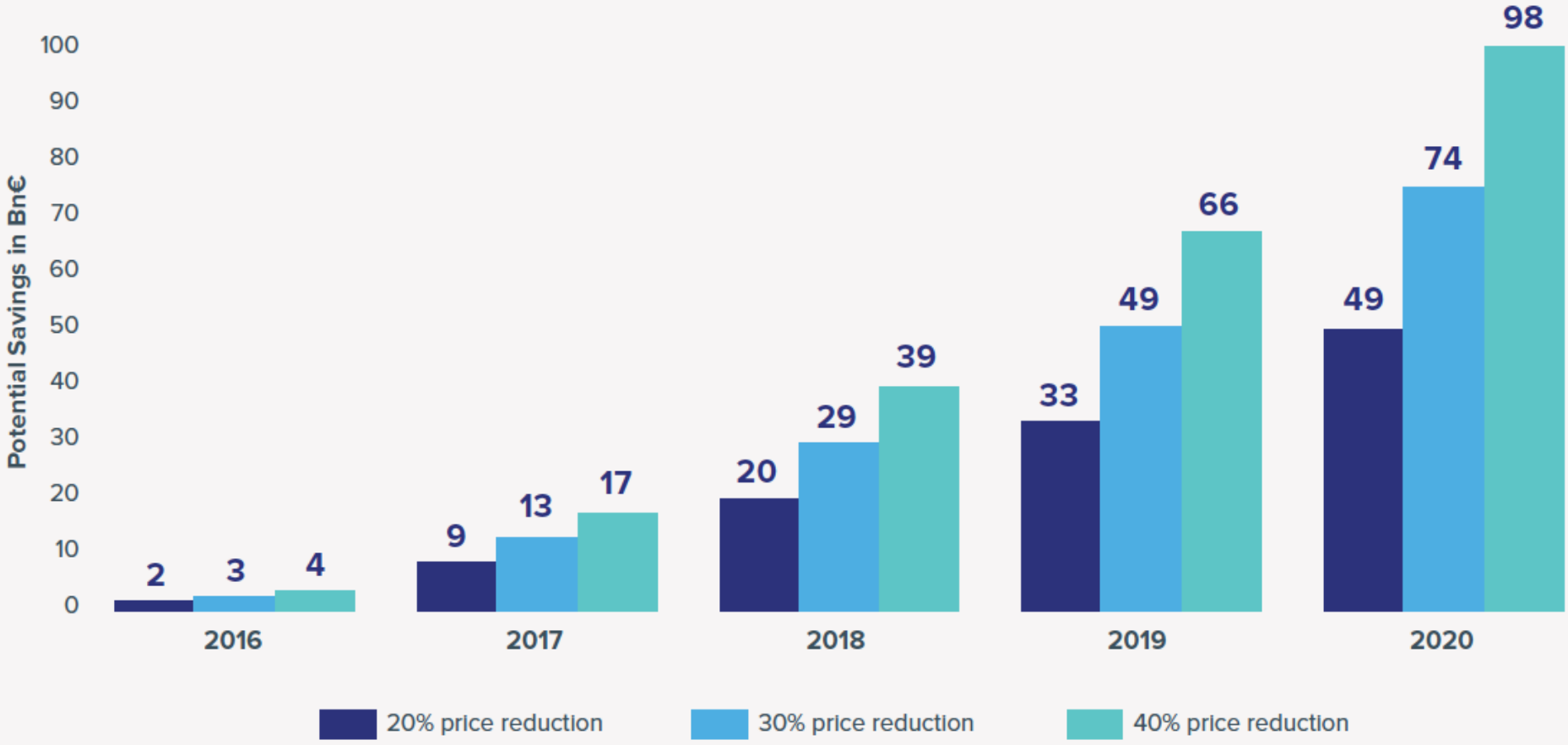


Comparability exercise

why?



Source: IMS Health, MIDAS, Dec 2015



Source: IMS Health, MIDAS, IMS Health Market Prognosis; IMS Institute for Healthcare Informatics, Dec 2015

Biosimilars: How Can Payers Get Long-Term Savings?

Jorge Mestre-Ferrandiz[1] · Adrian Towse[1] · Mikel Berdud[1]

PharmacoEconomics (2016) 34:609–616

development costs

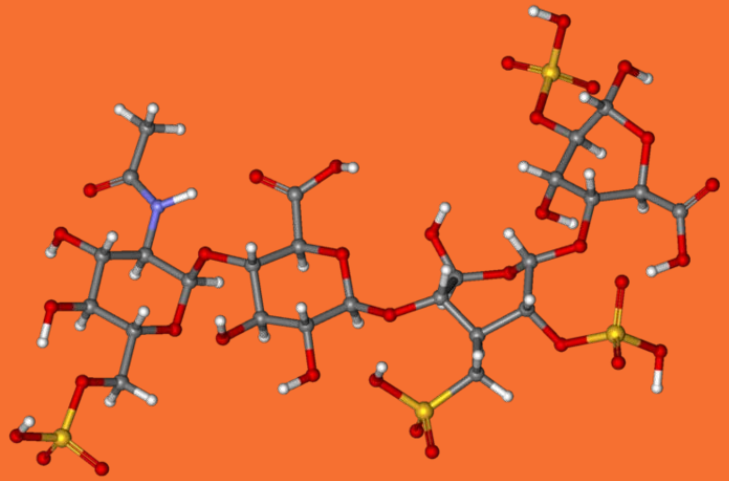
manufacturing costs

barriers to entry

need for post-launch data

degree of competition

and the heparins?



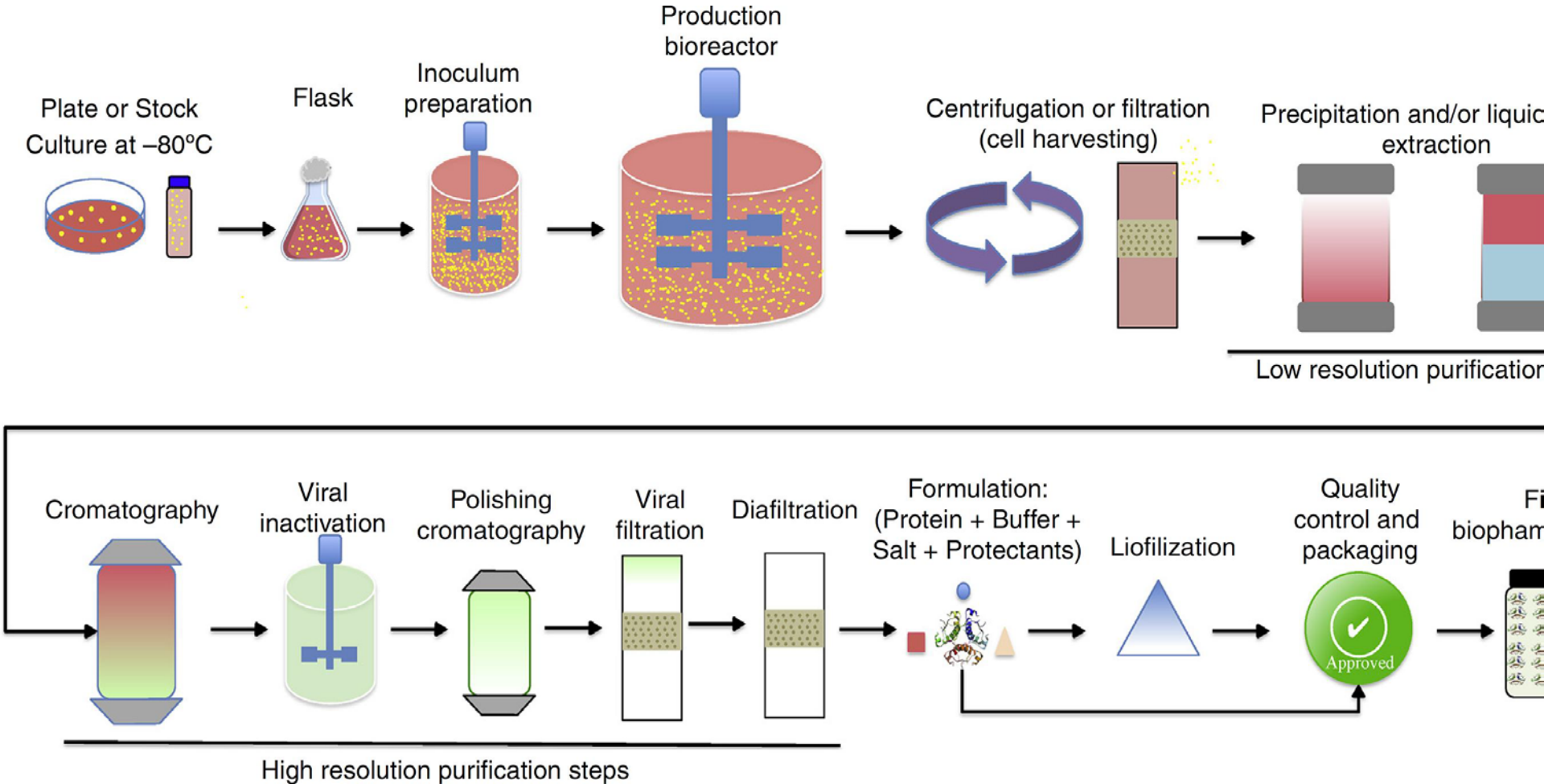
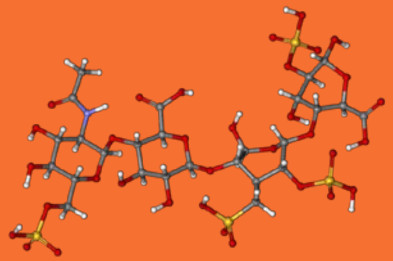
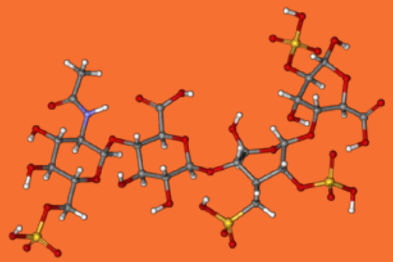


Plate or Stock Culture at –80°C
Flask
Inoculum preparation
Production bioreactor
Centrifugation or filtration (cell harvesting)
Precipitation and/or liquic extraction
Low resolution purification
Cromatography
Viral inactivation
Polishing cromatography
Viral filtration
Diafiltration
Formulation: (Protein + Buffer + Salt + Protectants)
Liofilization
Quality control and packaging
Approved
Fi biopham
High resolution purification steps



Heparin Manufacturing Process

		Description	Impurities Removed
STEP 1	Extraction	▪ Porcine intestines collected from slaughter houses and mucosa extracted ▪ Mucosa digested with enzymes	
STEP 2	Separation	▪ Separation of polysaccharide material ▪ Complex with resins or charged ammonium salts (heparin concentration step) ▪ Crude heparin released from resins ▪ Precipitation of heparin with water miscible organic solvents	Neutral and positively charged impurities, peptides and DNA impurities, lipids
STEP 3	Purification	▪ Acid and base wash (viral inactivation) ▪ H_2O_2, $KMnO_4$ or peracetic treatment (chemical oxidation and viral inactivation step) ▪ Alcohol/water precipitation (See Precipitation of heparin above) ▪ Multiple refractionation ▪ Drying	Protein and DNA impurities, viruses, bacterial endotoxins, related glycosaminoglycans



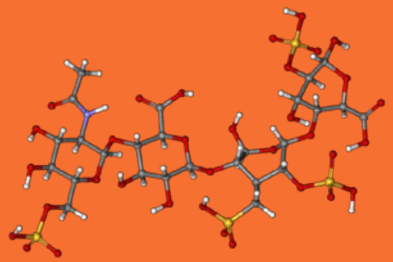
CHEMICAL DRUG

EQUIVALENT

FDA criteria for demonstration of sameness with enoxaparin

Equivalence:

- of physicochemical properties
- of source material and method of depolimerization
- in nature and arrangement of saccharide components
- in certain measures of anticoagulant activity
- in certain aspects of the drug's effect in humans

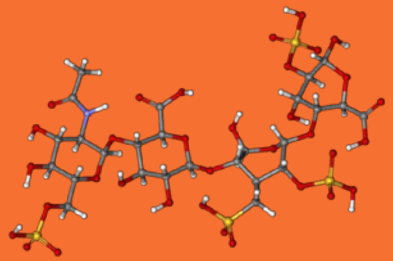


CHEMICAL DRUG

EQUIVALENT

BIOLOGIC

BIOSIMILAR



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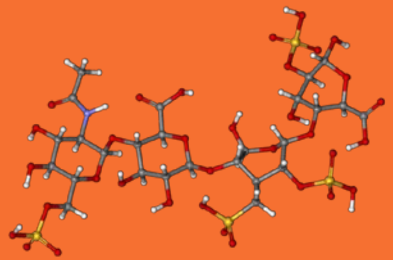
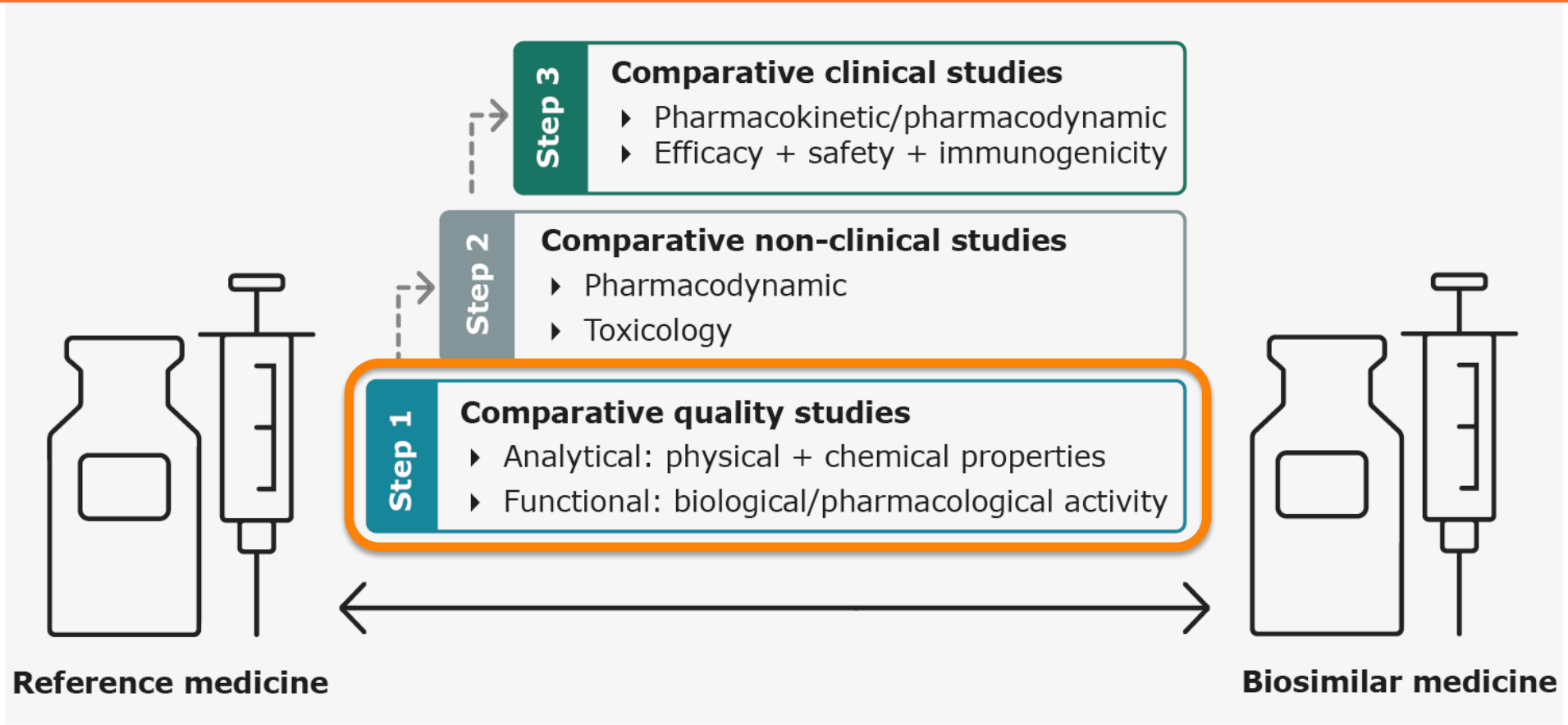


INHIXA
THORINANE

ENOXAPARINA ROVI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Comparative clinical studies
Pharmacokinetic/pharmacodynamic
Efficacy + safety + immunogenicity
Step 2
Comparative non-clinical studies
Pharmacodynamic
Toxicology
Step 1
Comparative quality studies
Analytical: physical + chemical properties
Functional: biological/pharmacological activity
Reference medicine
Biosimilar medicine

Structural and functional analyses of biosimilar enoxaparins available in Brazil

Stephan-Nicollas M. C. G. Oliveira; Gustavo R. C. Santos; Bianca F. Glauser; Nina V. M. Capillé; Ismael N. L. Queiroz; Mariana S. Pereira; Vitor H. Pomin; Paulo A. S. Mourão

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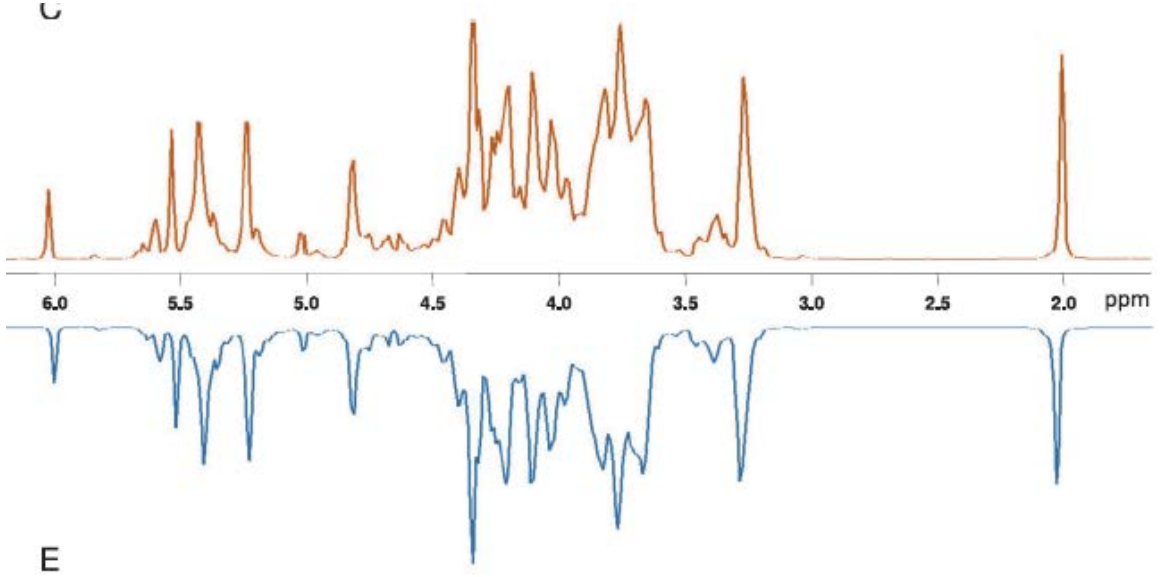
Thrombosis and Haemostasis 113.1/2015



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Thrombosis and Haemostasis 113.1/2015

dp**	Oligossacharides distribution (% of total)*			
	A_{232nm}		RI	
	Parental drug	Biosimilar	Parental drug	Biosimilar
≤4	14.0 ± 1.4	16.8 ± 2.2	5.1 ± 0.4	5.9 ± 0.6
6	19.4 ± 0.6	19.7 ± 1.5	11.3 ± 0.3	11.5 ± 0.4
8	17.3 ± 0.4	16.5 ± 1.2	12.8 ± 0.2	12.5 ± 0.3
10	12.9 ± 0.4	12.9 ± 1.0	12.4 ± 0.2	13.2 ± 0.2
12	9.7 ± 0.3	9.7 ± 0.9	11.08 ± 0.2	11.4 ± 0.2
14	8.1 ± 0.3	7.3 ± 0.6	9.5 ± 0.2	8.5 ± 0.2
≥16	18.6 ± 1.5	17.0 ± 1.6	37.7 ± 1.4	37.2 ± 1.7
	*NS***		*NS***	

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

21 July 2016
EMA/536977/2016
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Inhixa

An extensive comparison strategy has been carried out in order to demonstrate the biosimilarity of the test Enoxaparin sodium injection and the reference product Clexane. Biosimilarity comparisons have involved broad physico-chemical properties, oligosaccharide chain characterisation, and molecular weight determinations which show Enoxaparin Sodium to be within the reference range of Clexane. Assessment of various monosaccharide building blocks in the enoxaparin chain was also carried out with a range of orthogonal techniques.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

21 July 2016
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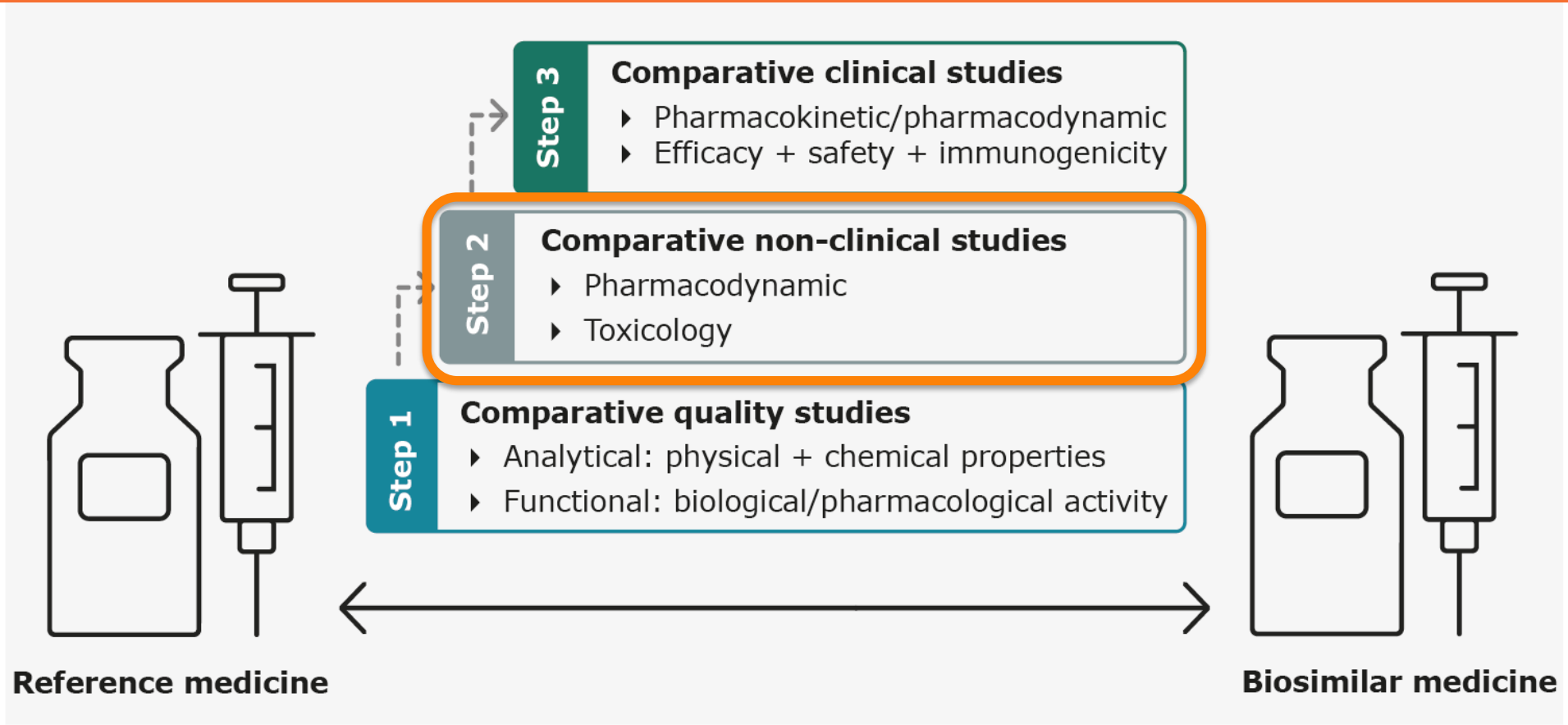
Assessment report

Inhixa

A number of *in-vitro* tests that assess inhibition of coagulation factors Xa (anti-FXa) and IIa (anti-FIIa), and clotting tests such as activated partial thromboplastin time (aPTT) and HEPTEST have also been compared between the test Enoxaparin sodium injection and Clexane formulations. The aPTT and HEPTEST assay results were compared using an equivalency test. The data in general show the test results to be comparable.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Efficacy + safety + immunogenicity
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EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

21 July 2016
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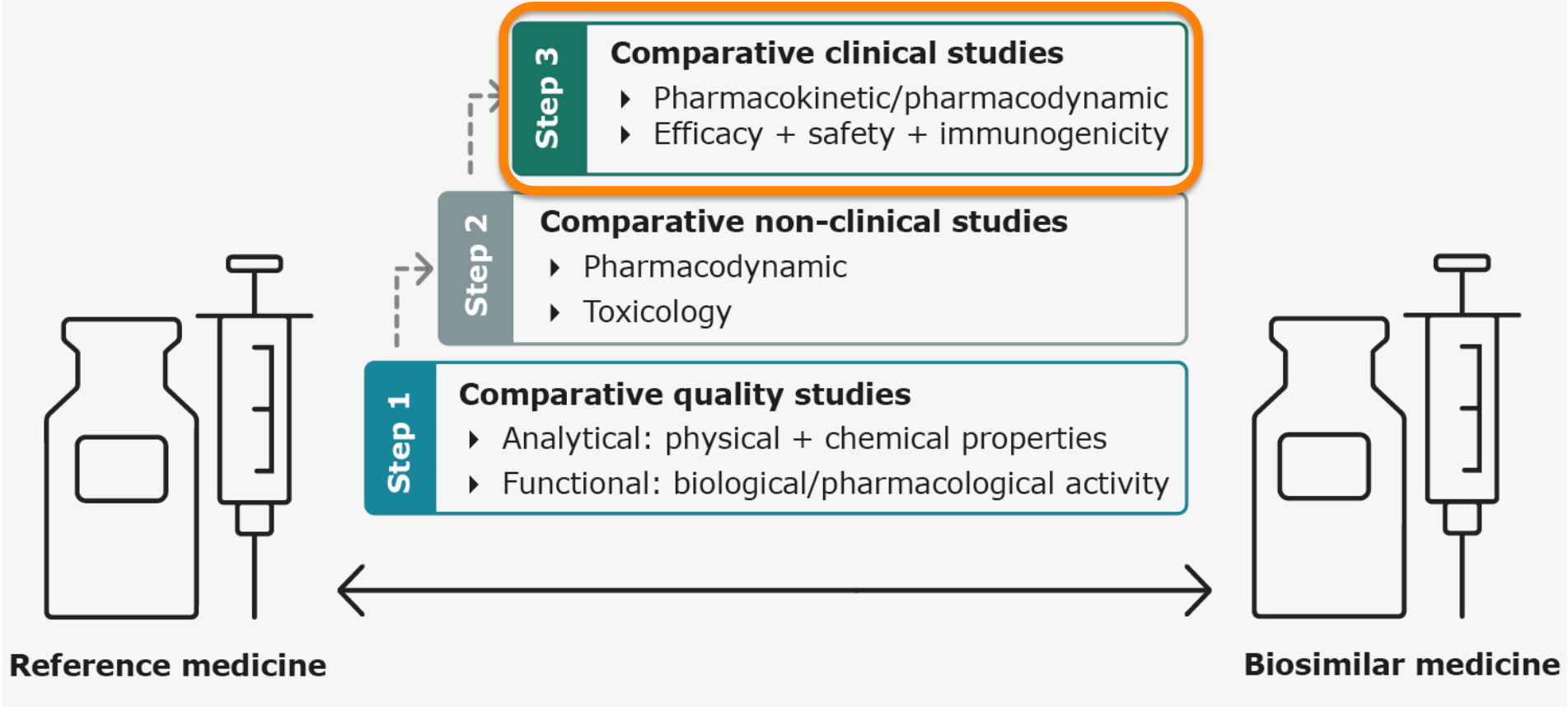
Assessment report

Inhixa

With responses the applicant submitted PF4-LMWH and PF4 analysis by SEC, In-vitro PBMC (peripheral blood mononuclear cell) model and the results of measuring serotonin release as detected after adding PF4-enoxaparin complexes.

2.3.7. Conclusion on the non-clinical aspects

The CHMP concluded that from the non-clinical perspective relevant assays were conducted and were **not able to identify different immunogenic potential** for the biosimilar candidate when compared to the RMP. The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Assessment report

Inhixa

2.4.3.7. Comparative PK/PD Trial: Study No 411/13 (EudraCT No.: 2013-002864-21)

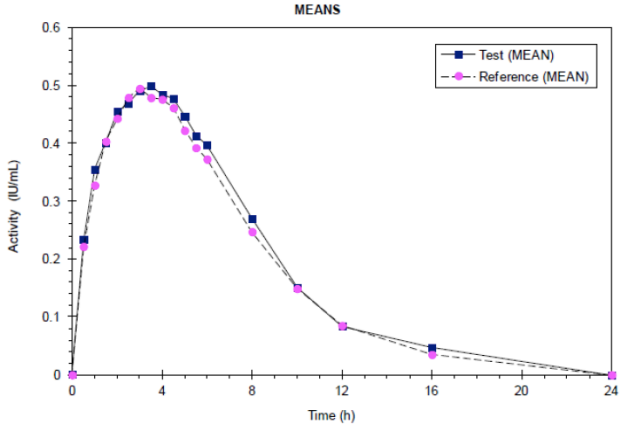
The applicant submitted a single comparative pharmacodynamic (PD) bioequivalence study comparing Enoxaparin sodium 40 mg/0.4 ml solution for injection to Clexane 40 mg/0.4 ml solution for injection via subcutaneous administration in 20 healthy volunteers to support the demonstration of bioequivalence of Enoxaparin Inhixa to the reference medicinal product Clexane.

Study period: 11 October 20013- 21 October 2013

Date Report: 26 June 2014

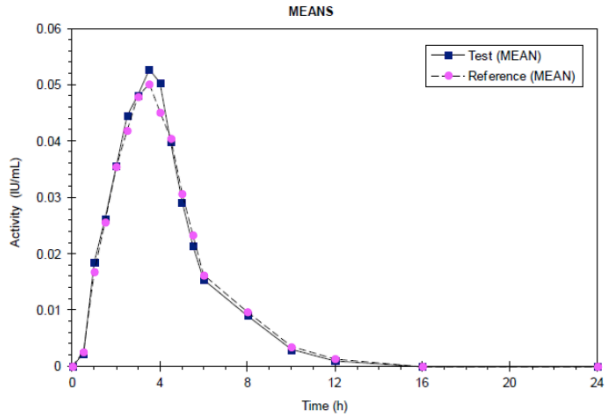
Pharmacokinetic Profile of Means:

Anti-Xa

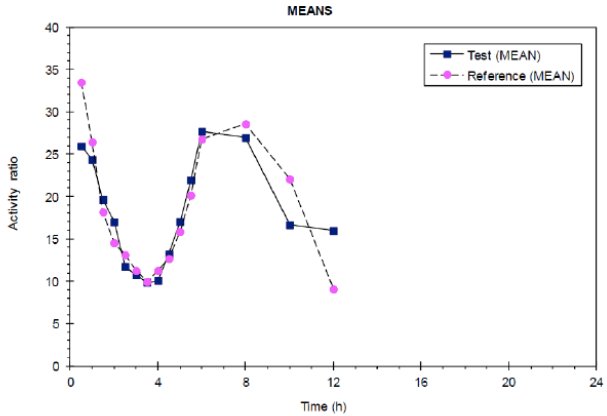


Pharmacokinetic Profile of Means:

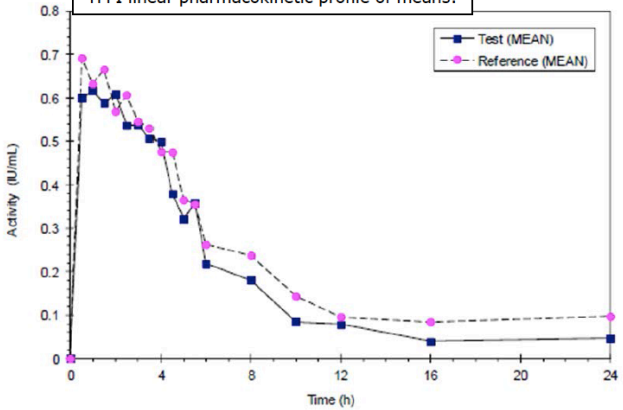
Anti-IIa



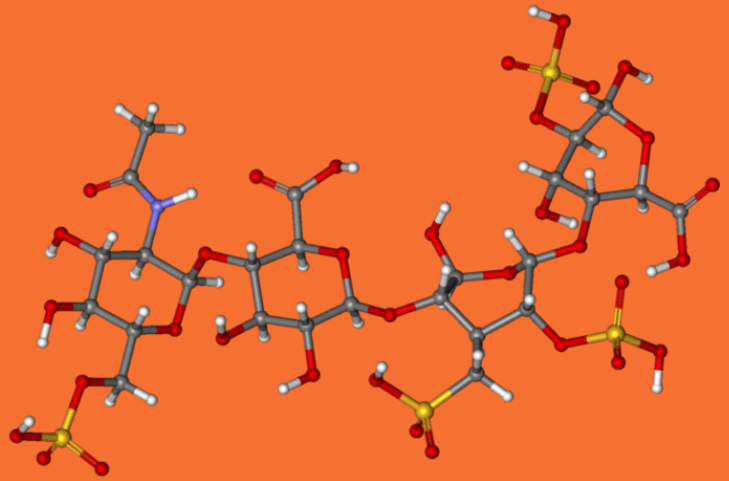
Anti-Xa/anti-IIa – Means of 20 Subjects (linear and semi-logarithmic scale)

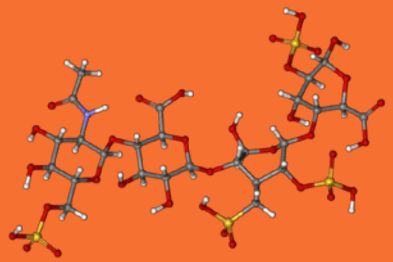


TFPI linear pharmacokinetic profile of means:



clinical efficacy





Update of the recommendations on biosimilar low-molecular-weight heparins from the Scientific Subcommittee on Control of Anticoagulation of the International Society on Thrombosis and Haemostasis

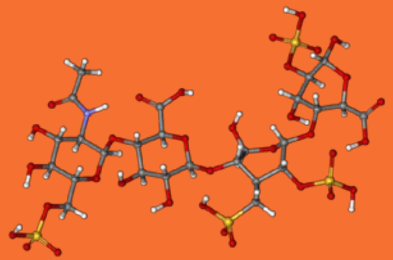
J. HARENBERG,* J. WALENGA,† G. TORRI,‡ O. E. DAHL,§¶ L. DROUET,** J. FAREED† and ON BEHALF OF THE SUBCOMMITTEE ON CONTROL OF ANTICOAGULATION OF THE SCIENTIFIC AND STANDARDIZATION COMMITTEE OF THE INTERNATIONAL SOCIETY ON THROMBOSIS AND HAEMOSTASIS

J Thromb Haemost 2013; 11: 1421–5.

Recommendation 5

As a first step, it needs to be demonstrated that the biosimilar LMWH and the originator LMWH have the same compositional profile. A product passing this test can move on to step 2, where preclinical investigations are to be performed (Recommendations 1–4). No impurities may be present on analysis using adequate methods. If these investigations do not identify differences, the biosimilar LMWH can be submitted to the authorities for approval. This approach is quite similar to the guidelines proposed by the FDA.

If differences between the originator and biosimilar version of an LMWH are detected by these investigations and if the producer of the biosimilar LMWH decides to further develop the product, one clinical study in postoperative venous thromboembolism (total knee/hip replacement surgery) and one clinical study in a cardiology setting (preferentially treatment of unstable angina) will be required. This recommendation is different from that of the FDA and similar to the revised draft EMEA guidelines [16]. A recommended solution is the development of a standard operating procedure for clinical trials by EMA, FDA and others to ensure comparability of the data.



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

17 January 2013

EMEA/CHMP/BMWP/118264/2007 Rev. 1
Committee for Medicinal products for Human (CHMP)

Guideline on non-clinical and clinical development of similar biological medicinal products containing low-molecular-weight-heparins

Draft

Clinical efficacy

A comparative clinical efficacy trial will usually be required as part of the comparability exercise. Only if similar efficacy of the biosimilar and the reference product can be convincingly deduced from the comparison of their physicochemical characteristics, biological activity/potency and PD fingerprint profiles, based on the use of highly sensitive and specific methods, then a dedicated efficacy trial may be waived. It is expected that this is an exceptional scenario since the required amount of reassurance from analytical data and bioassays would be considerable.

Therapeutic equivalence should be demonstrated in an adequately powered, randomised, double-blind, parallel group clinical trial. In theory, this could be done either in the setting of prevention of venous or arterial thromboembolism, or in the setting of treatment of venous thromboembolism. However, the most sensitive model to detect potential differences in efficacy between the biosimilar LMWH and the reference product should be selected.

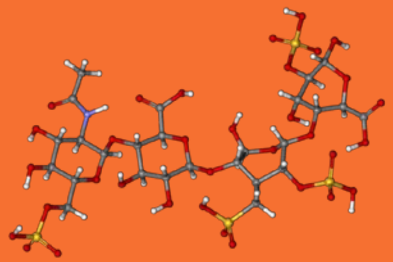
EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

21 July 2016
EMA/536977/2016
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Inhixa

During the CHMP Scientific Advice (SA) procedures, the applicant claimed that **PK/PD parameters** such as anti-Xa, anti-IIa and TFPI activities **are more sensitive to detect potential differences** in efficacy than clinical equivalence. This was endorsed by the CHMP since these biomarkers are predictive indicators of the pharmacologic action of LMWH. Furthermore efficacy trials do not seem to have enough sensitivity or statistical power to detect differences in clinical endpoints, since they have never been able to detect differences between different LMWH with evident differences in PK/PD and anti-FXa activity.



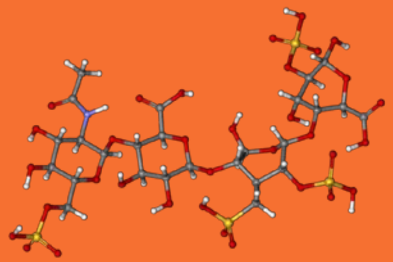
EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

10 November 2016
EMEA/CHMP/BMWP/118264/2007 Rev. 1
Committee for Medicinal products for Human (CHMP)

Guideline on non-clinical and clinical development of similar biological medicinal products containing low-molecular-weight-heparins

Clinical efficacy

Pivotal evidence for similar efficacy will be derived from the similarity demonstrated in physicochemical, functional and pharmacodynamic comparisons. A dedicated comparative efficacy trial is therefore not considered necessary.



The introduction of biosimilars of low molecular weight heparins in Europe: a critical review and reappraisal endorsed by the Italian Society for Haemostasis and Thrombosis (SISET) and the Italian Society for Angiology and Vascular Medicine (SIAPAV)

Davide Imberti[1], Marco Marietta[2], Hernan Polo Friz[3,4*] and Claudio Cimminiello[4]

Imberti *et al. Thrombosis Journal* (2017) 15:13

Abstract

Recently, the European Medicines Agency (EMA) authorized the introduction and marketing of Thorinane® and Inhixa®, biosimilars of the Low Molecular Weight Heparin (LMWH) enoxaparin. The authorization path is considerably different from the guidelines published by the EMA in 2009, as well as from the recommendations from the International Society on Thrombosis and Haemostasis published in 2013. Indeed, both of them recommended that LMWHs biosimilars therapeutic equivalence should be demonstrated in at least one adequately designed clinical trial. Shortly after enoxaparin biosimilars approval, EMA published a revised version of its guideline, no longer requiring the execution of a clinical study in patients at risk of venous thromboembolism.

Also the assessment of safety shows some relevant flaws, as it relies only on a 20 healthy volunteers study, clearly underpowered to draw any conclusions about the safety profile of the drug.

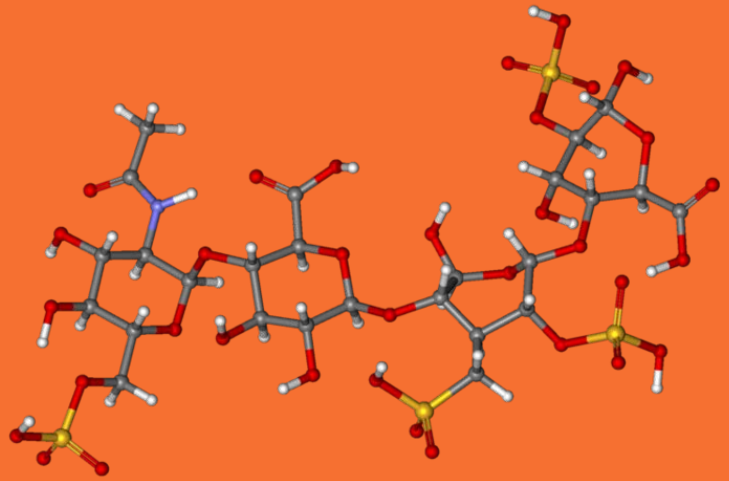
In our opinion, the approach taken by EMA for approval of enoxaparin biosimilars raises serious concerns about their actual, clinical "similarity".

On these grounds, with the endorsement of the Italian Society for Haemostasis and Thrombosis (SISET) and the Italian Society for Angiology and Vascular Medicine (SIAPAV), we elaborated the present document aimed at reviewing and reappraising some critical points regarding the introduction of biosimilars of LMWH in Europe.

Moreover, we would strongly advise the Italian National Health Authorities not to entrust safety assessment to the post-marketing surveillance only, but to promote well designed and powered studies aimed at establish the actual efficacy and safety of LMWH biosimilars.

Keywords: Low molecular weight heparin, Biosimilar pharmaceuticals, Evidence-based practice, Therapeutic equivalency, Venous Thromboembolism

clinical safety



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

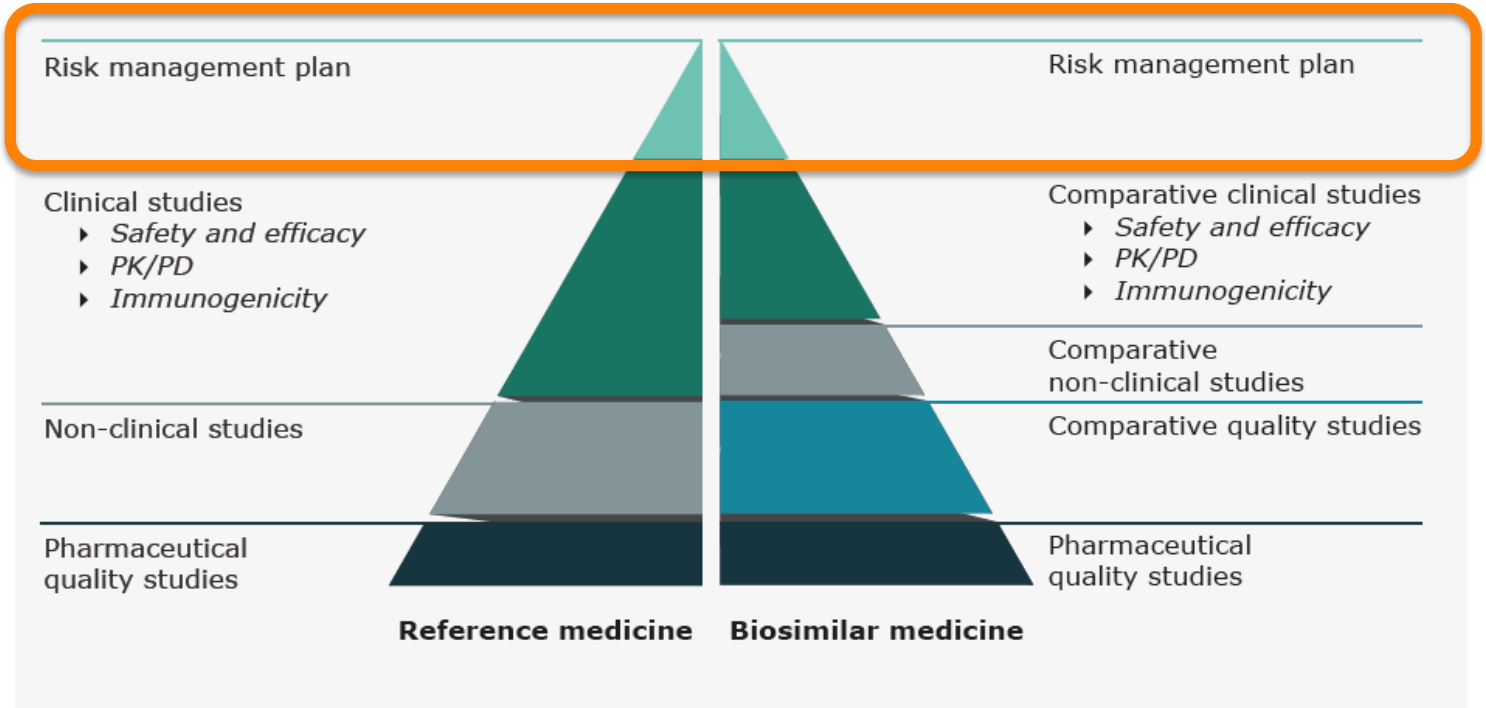
21 July 2016
EMA/536977/2016
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Inhixa

Patient exposure

Twenty (20) healthy volunteers received a single dose of 40 mg enoxaparin s.c. (test and reference product in a cross-over design) in each of 2 study periods with a wash-out period of 8 days in between. All subjects screened were exposed to investigational product in period 01 and period 02 as foreseen. There were no drop outs or withdrawals.

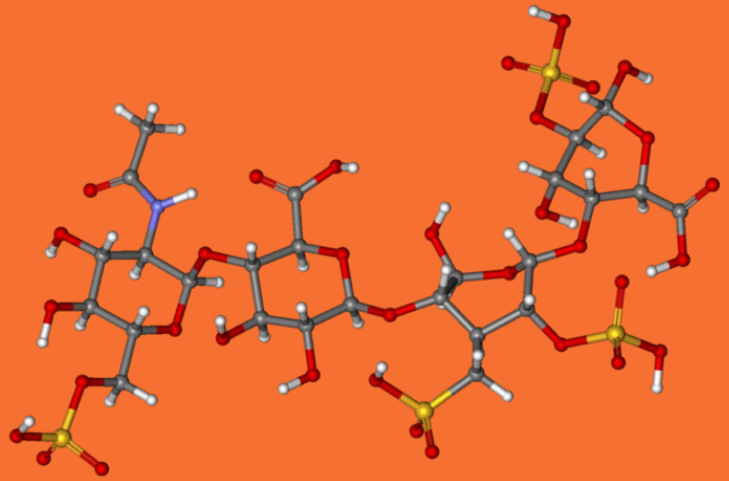

Risk management plan
Clinical studies
Safety and efficacy
PK/PD
Immunogenicity
Non-clinical studies
Pharmaceutical quality studies
Reference medicine
Risk management plan
Comparative clinical studies
Safety and efficacy
PK/PD
Immunogenicity
Comparative non-clinical studies
Comparative quality studies
Pharmaceutical quality studies
Biosimilar medicine

▼Medicinale sottoposto a monitoraggio addizionale. Ciò permetterà la rapida identificazione di nuove informazioni sulla sicurezza. Agli operatori sanitari è richiesto di segnalare qualsiasi reazione avversa sospetta. Vedere paragrafo 4.8 per informazioni sulle modalità di segnalazione delle reazioni avverse.

1. DENOMINAZIONE DEL MEDICINALE

Inhixa 2.000 UI (20 mg)/0,2 ml soluzione iniettabile

extrapolation of indications



10 November 2016
EMEA/CHMP/BMWP/118264/2007 Rev. 1
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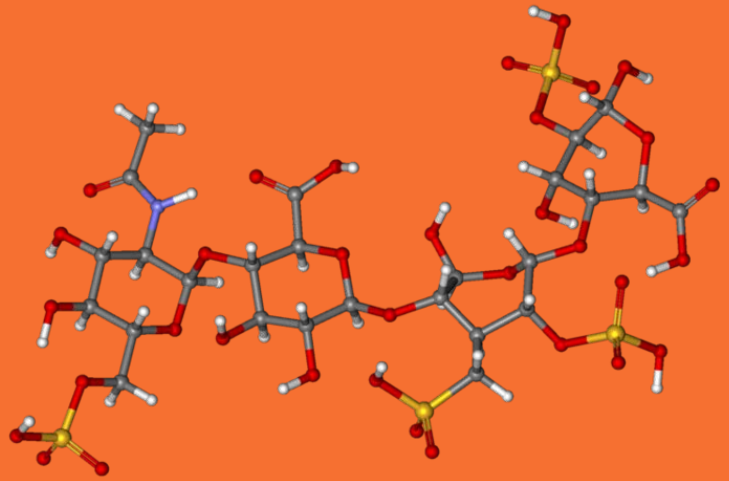
Guideline on non-clinical and clinical development of similar biological medicinal products containing low-molecular-weight-heparins

8. Extrapolation of indication

Demonstration of biosimilarity, based on physicochemical and functional characterisation, pharmacodynamic profiles, and, where needed, safety/immunogenicity trial, will allow extrapolation to other routes of administration and indications licensed for the reference medicinal product, if applicable and appropriately justified.

- Profilassi del tromboembolismo venoso (TEV) nei pazienti chirurgici a rischio moderato e alto, in particolare quelli sottoposti a chirurgia ortopedica o generale, compresa la chirurgia oncologica.
- Profilassi del tromboembolismo venoso in pazienti non chirurgici affetti da una patologia acuta (come ad esempio insufficienza cardiaca acuta, insufficienza respiratoria, infezioni gravi o malattie reumatiche) e mobilità ridotta ad aumentato rischio di tromboembolismo venoso.
- Trattamento della trombosi venosa profonda (TVP), dell'embolia polmonare (EP) o entrambi, ad esclusione della EP che potrebbe richiedere terapia trombolitica o chirurgica.
- Prevenzione della formazione di trombi nella circolazione extracorporea in corso di emodialisi.
- Sindrome coronarica acuta:
  - Trattamento dell'angina instabile e dell'infarto del miocardio senza sopraslivellamento del tratto ST (NSTEMI) in associazione con acido acetilsalicilico orale.
  - Trattamento dell'infarto miocardico acuto con sopraslivellamento del tratto ST (STEMI), inclusi i pazienti gestiti con la sola terapia farmacologica o da sottoporre a successivo intervento coronarico percutaneo (PCI).

interchangeability



Interchangeability refers to the possibility of exchanging one medicine for another medicine that is expected to have the same clinical effect. This could mean replacing a reference product with a biosimilar (or vice versa) or replacing one biosimilar with another. Replacement can be done by:

- **Switching**, which is when the prescriber decides to exchange one medicine for another medicine with the same therapeutic intent.

- **Substitution** (automatic), which is the practice of dispensing one medicine instead of another equivalent and interchangeable medicine at pharmacy level without consulting the prescriber.

EMA and Member States' responsibilities

When EMA carries out the scientific review of a biosimilar, the evaluations do not include recommendations on whether the biosimilar is interchangeable with the reference medicine, and thus whether the reference medicine can be switched or substituted with the biosimilar.

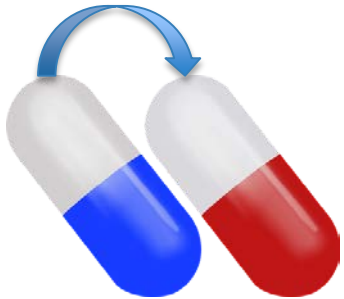
The decision on whether to allow interchangeable use and substitution of the reference biological medicine and the biosimilar is taken at national level. Information on the scientific evaluation performed by EMA's scientific committees is available on EMA's website and could be used to support decisions.

Agenzia Italiana del Farmaco

AIFA

Secondo Position Paper AIFA sui Farmaci Biosimilari

Come dimostrato dal processo regolatorio di autorizzazione, il rapporto rischio-beneficio dei biosimilari è il medesimo di quello degli originatori di riferimento. Per tale motivo, l'AIFA considera i biosimilari come prodotti intercambiabili con i corrispondenti originatori di riferimento. Tale considerazione vale tanto per i pazienti *naïve* quanto per i pazienti già in cura.



Agenzia Italiana del Farmaco

AIFA

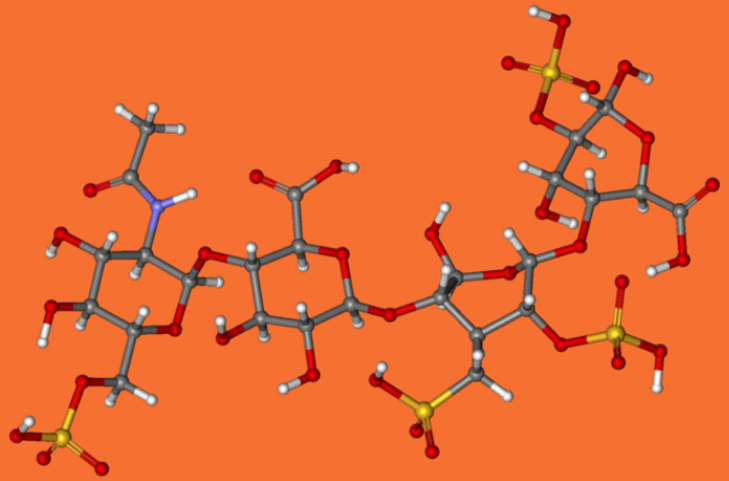
Secondo Position Paper AIFA sui Farmaci Biosimilari

Pur considerando che la scelta di trattamento rimane una decisione clinica affidata al medico prescrittore, a quest'ultimo è anche affidato il compito di contribuire a un utilizzo appropriato delle risorse ai fini della sostenibilità del sistema sanitario e la corretta informazione del paziente sull'uso dei biosimilari.

Secondo Position Paper AIFA sui Farmaci Biosimilari

In Italia la posizione dell'AIFA chiarisce che i medicinali biologici e biosimilari non possono essere considerati *sic et simpliciter* alla stregua dei prodotti generici, o equivalenti.

legge 648/1996



Agenzia Italiana del Farmaco
AIFA

Secondo Position Paper AIFA sui Farmaci Biosimilari

Anche i prodotti biologici possono essere utilizzati per l'uso *off-label*, e quindi nel caso di un medicinale biosimilare il cui corrispondente medicinale biologico di riferimento sia già stato autorizzato per l'utilizzo *off-label* e sia, quindi, presente nel richiamato elenco, l'inserimento del biosimilare non è automatico, ma viene verificato caso per caso dalla CTS, che si riserva la possibilità di esprimere il proprio parere sulla base delle evidenze scientifiche e della letteratura disponibili, dell'esperienza clinica e dell'eventuale riconducibilità dell'azione terapeutica ad un identico meccanismo d'azione.

Conclusions

Involved in economic NHS sustainability

Confident on pre-clinical aspects

Active on pharmacovigilance

Thank you