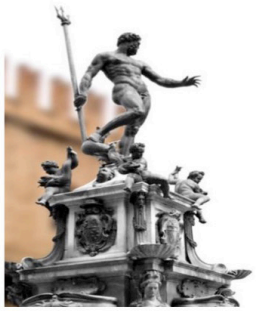


Ruolo attuale e prossime novità per le eparine a basso peso molecolare (EPBM)

L'approvazione di eparine biosimilari

Cimminiello C. – Carate Brianza (MB)

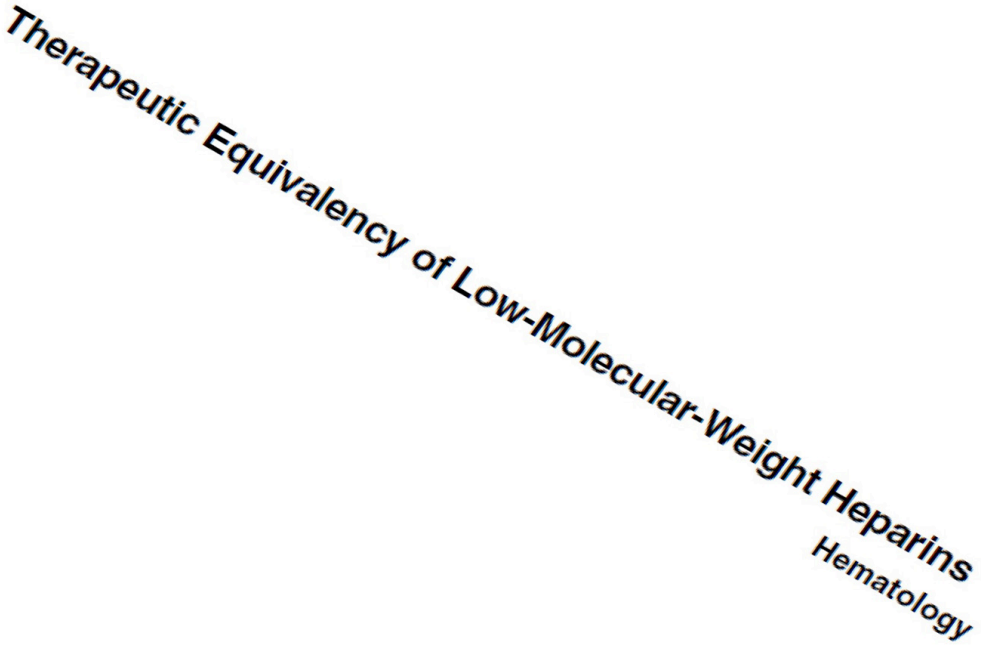
Il sottoscritto Claudio Cimminiello
ai sensi dell'art. 3.3 sul Conflitto di Interessi, pag. 17 del Reg. Applicativo dell'Accordo Stato-Regione del 5 novembre 2009,

dichiara

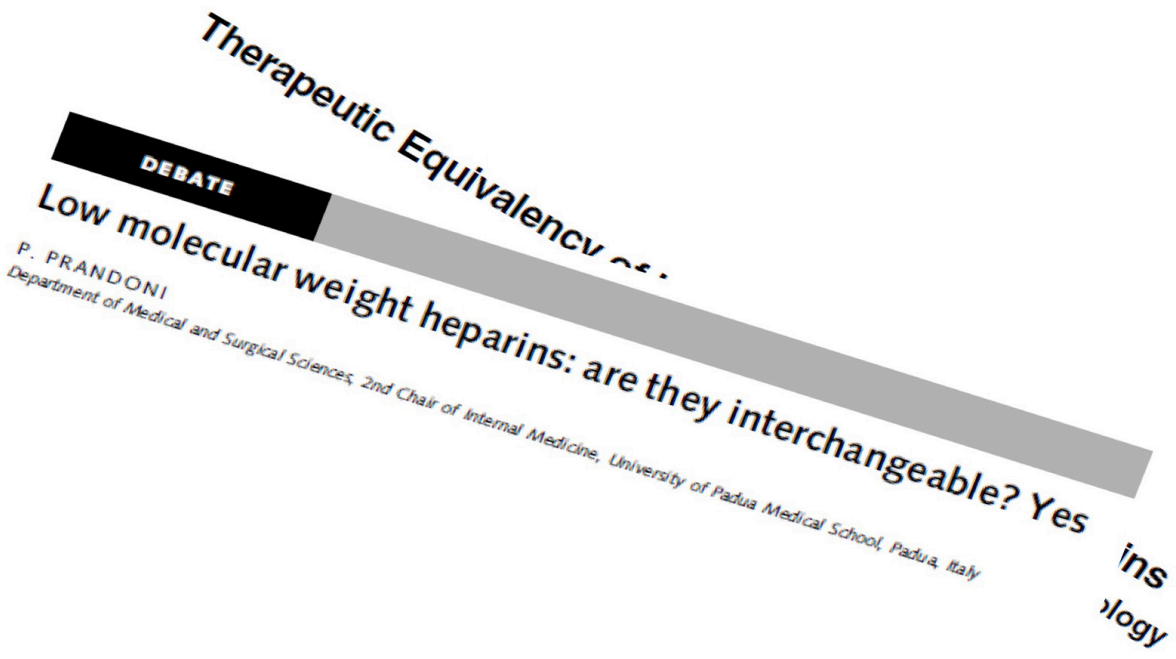
che negli ultimi due anni ha ricevuto onorari per relazioni a congressi e consulenza con i seguenti soggetti portatori di interessi commerciali in campo sanitario:

- *AstraZeneca*
- *BMS/Pfizer*
- *Sanofi*
- *MSD*
- *BAYER*
- *Boehringer Ingelheim*

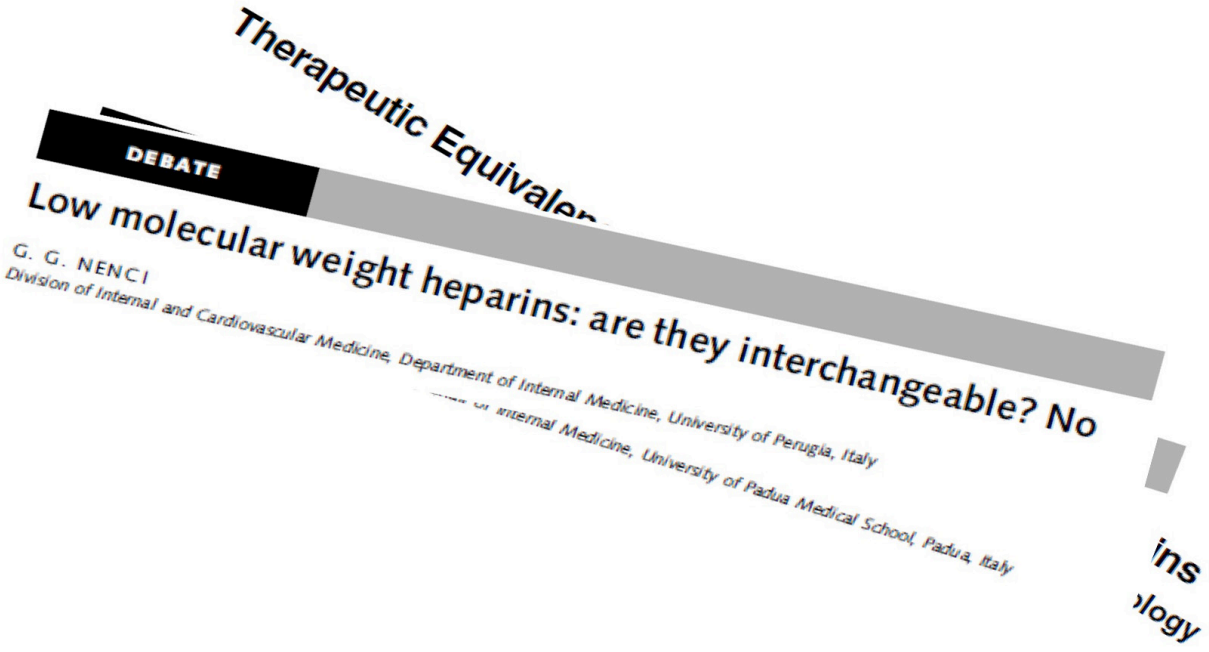
LMWHs Are They All the Same?



LMWHs Are They All the Same?



LMWHs Are They All the Same?



Arrivano i nostri!!!

Four Generic Enoxaparins have entered the US market:

Amphastar
Sandoz
Winthrop
Chemi/Teva

LMWH PRODUCTS AND THEIR COPIES: THE TWO DIFFERENT APPROACHES OF FDA AND EMA

- FDA classifies LMWHs as semi-synthetic products
- EMA classifies LMWHs as biological products

LMWH PRODUCTS AND THEIR COPIES: THE TWO DIFFERENT APPROACHES OF FDA AND EMA

FDA approves a copy of an LMWH originator if five criteria are met

(i) heparin source

(ii) method of depolymerization

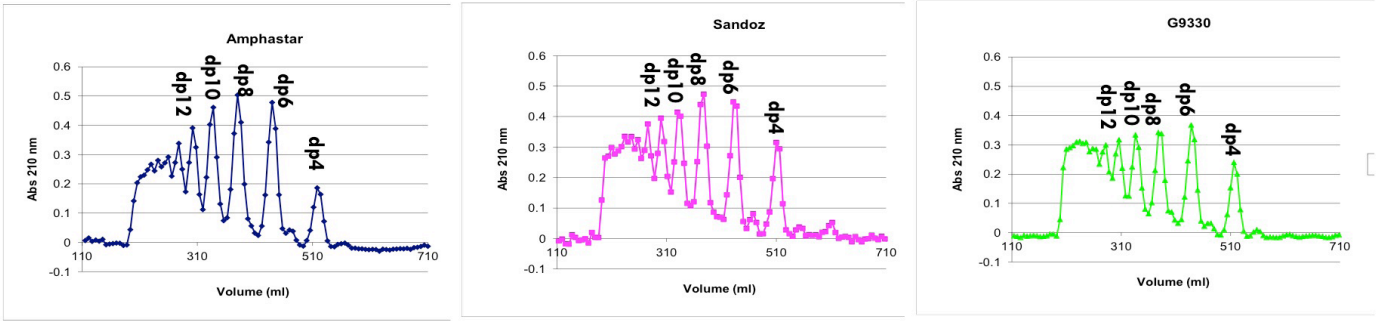
(iii) basic disaccharide unit of specific polysaccharide fragments and specific sequences of oligosaccharides

(iv) biological and biochemical evaluation tests

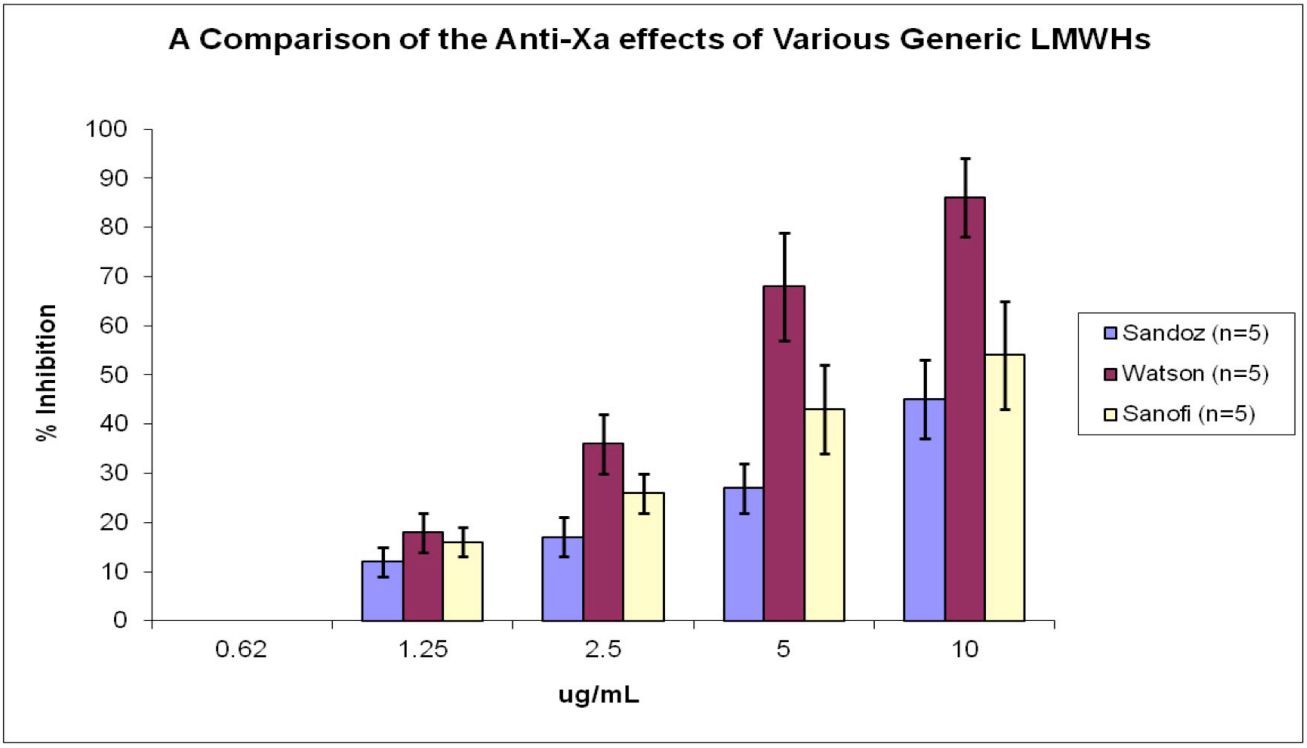
(v) in vivo equivalence of the pharmacodynamics profile

Size-homogeneous chromatographic fractions

Gel permeation elution profiles on Bio-gel P6 of enoxparins



				Area %				
Sample	>Dodeca	Dodeca	Deca	Octa	Hexa	Penta	Tetra	<Tetra
Amphastar	32.2	8.6	15.0	17.8	15.5	2.0	7.2	1.5
Sandoz	34.3	9.4	10.2	16.4	13.4	1.8	9.7	4.9
Lovenox	40.2	7.8	11.8	15.0	14.3	1.1	8.7	1.2



Walenga JM Clin Appl Thromb Hemost. 2013;19:261-7.

LMWH PRODUCTS AND THEIR COPIES: THE TWO DIFFERENT APPROACHES OF FDA AND EMA

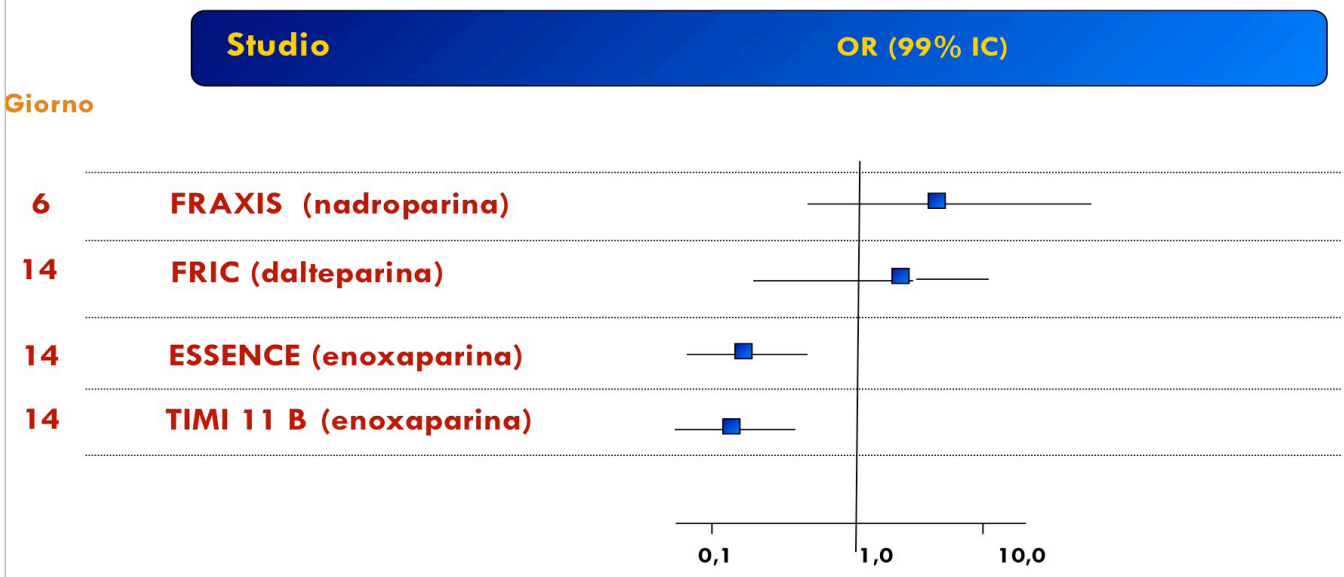
EMA requires in addition to phase I studies using anti-factor Xa and anti-thrombin assays:

i) Studies on activated partial thromboplastin time, prothrombin time, release of tissue factor pathway inhibitor

ii) assessment of the formation of PF4 antibodies and the occurrence of heparin-induced thrombocytopenia (HIT-II)

iii) At least one adequately powered, randomized, double-blind and parallel group clinical trial in the setting of prevention of VTE or arterial thromboembolism or treatment of VTE.

EBPM nelle Sindromi Coronariche Acute: effetti sul Triplo End-point

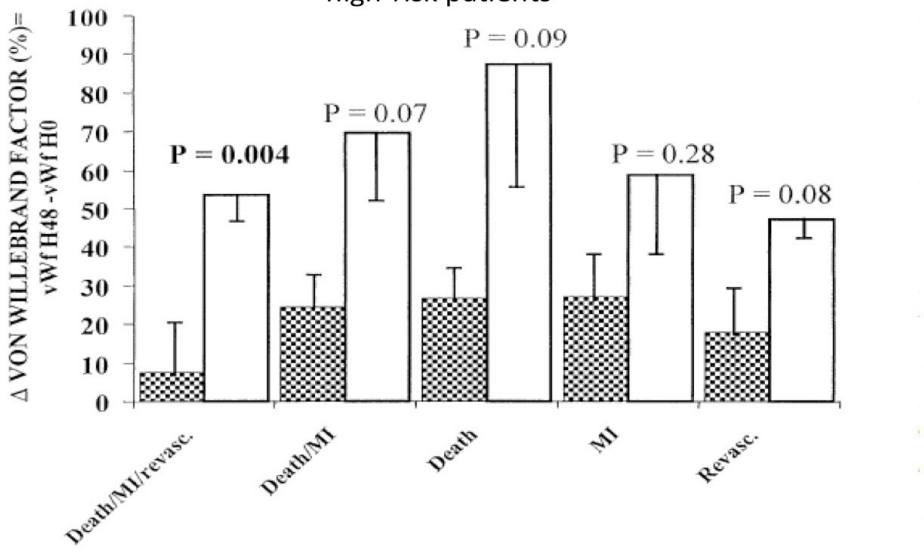


ACC/AHA Guidelines 2002

Effects of Various Anticoagulant Treatments on von Willebrand Factor Release in Unstable Angina

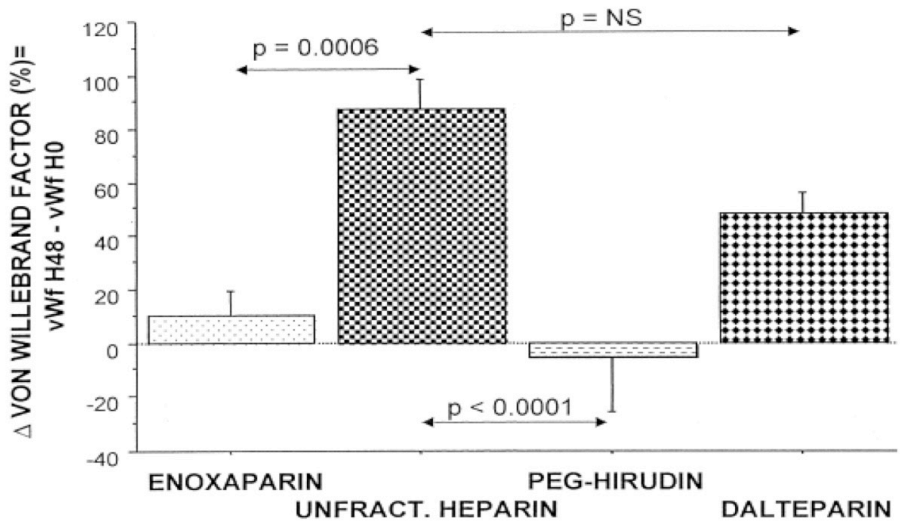
JACC

The rise of von Willebrand factor over the first 48 h identified high-risk patients



Montalescot G et al JACC 2000; 36:110-4

Effects of Various Anticoagulant Treatments on von Willebrand Factor Release in Unstable Angina



Montalescot G et al JACC 2000; 36:110-4

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Contaminated Heparin Associated with Adverse Clinical Events and Activation of the Contact System

Kishimoto TK. N Engl J Med 2008;358:2457-67.

LE RACCOMANDAZIONE ISTH SUI BIOSIMILARI DI EBPM

Journal of Thrombosis and Haemostasis, **11**: 1421–1425 DOI: 10.1111/jth.12269

OFFICIAL COMMUNICATION OF THE SSC

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

**Clinical Pharmacology, Medical Faculty Mannheim, University of Heidelberg, Heidelberg, Germany; †Department of Pathology and Cardiovascular Disease, Loyola University Medical Center, Maywood, IL, USA; ‡G. Ronzoni Institute for Chemical and Research, Milan, Italy; §Innlandet Hospital Trust, Brumunddal, Norway; ¶Thrombosis Research Institute, London, UK; and **Department of Angiohematology, Hospital Lariboisiere, Paris, France*

Journal of Thrombosis and Haemostasis, **13**: 1–6 DOI: 10.1111/jth.13237

FORUM

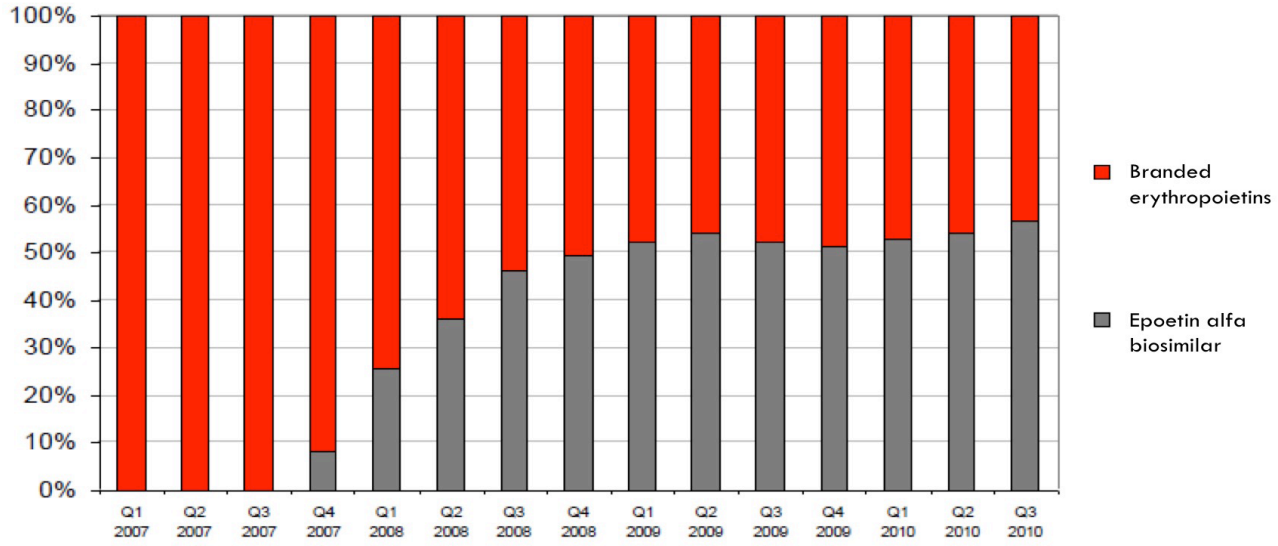
Biosimilars of low-molecular-weight heparin products: fostering competition or reducing 'biodiversity'?

J. HARENBERG,* C. CIMMINIELLO,† G. AGNELLI,‡ G. DI MINNO,§ H. POLO FRIZ,† P. PRANDONI¶ and F. SCAGLIONE**

**Clinical Pharmacology, Medical Faculty Mannheim, Ruprecht-Karls University Heidelberg, Mannheim, Germany; †Department of Medicine, Vimercate Hospital Azienda Ospedaliera di Desio e Vimercate, Vimercate; ‡Internal and Cardiovascular Medicine Stroke Unit, University of Perugia, Perugia; §Department of Clinical and Experimental Medicine, Federico II University Hospital, Naples; ¶Department of Cardiothoracic and Vascular Sciences, Clinica Medica 2, University of Padua, Padua; and **Department of Medical Biotechnology and Translational Medicine, University of Milan, Milan, Italy*

Biosimilars: the issue of biodiversity

Germany EPOETIN ALFA biosimilars penetration in value within total molecule sales

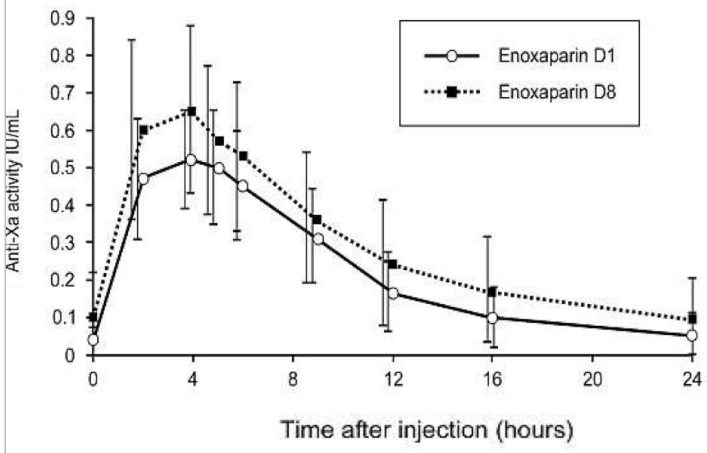


Source: IMS Health, IMS MIDAS – Q3 2010
Sales in Value (CHF)

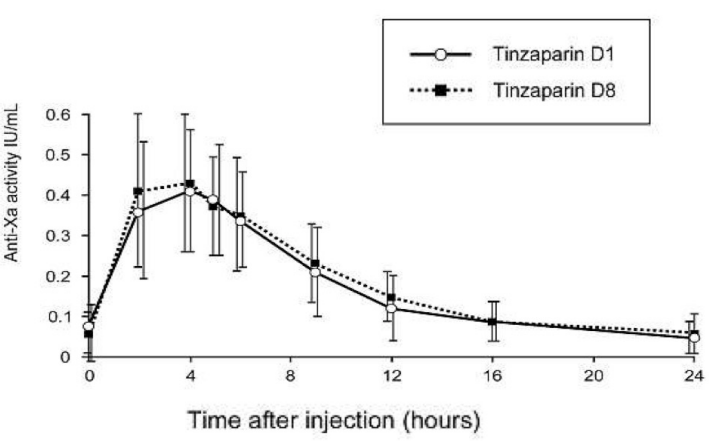
Biosimilars: the issue of biodiversity

Tinzaparin and enoxaparin given at prophylactic dose for eight days in medical elderly patients with impaired renal function

Anti-Xa activity on Day 1 and Day 8 in Enoxaparin group

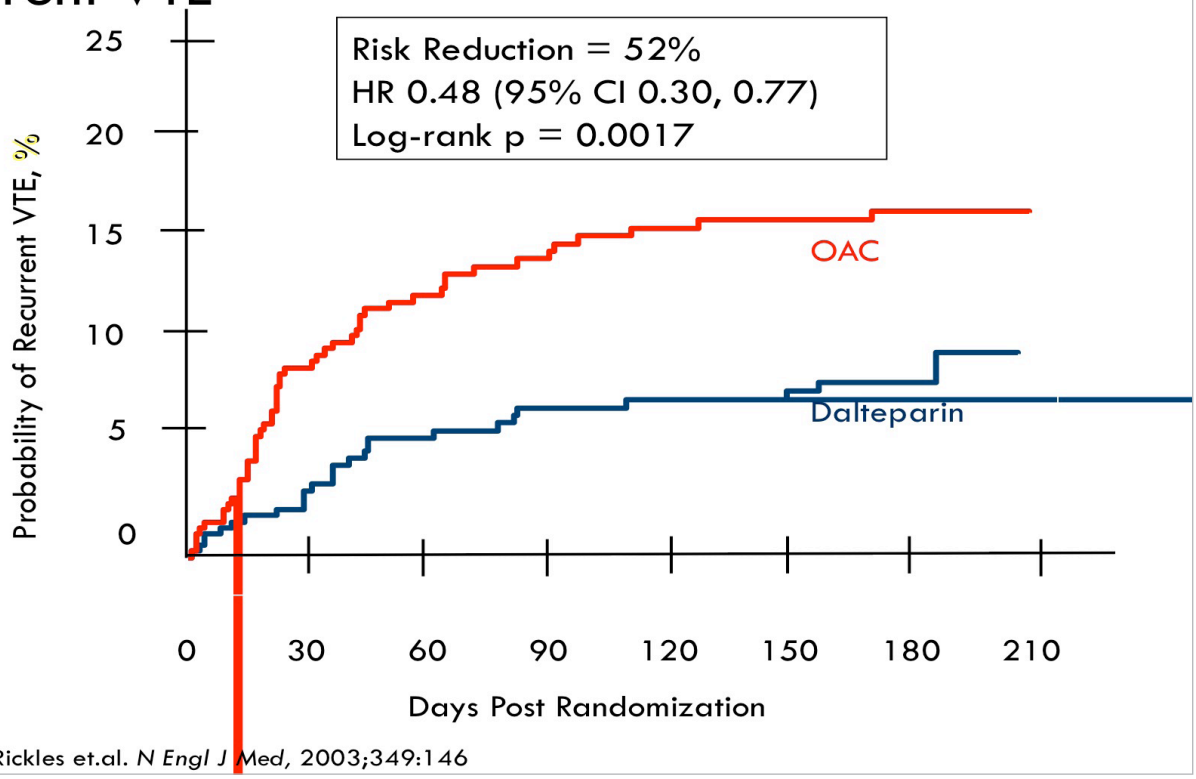


Anti-Xa activity on Day 1 and Day 8 in Tinzaparin group

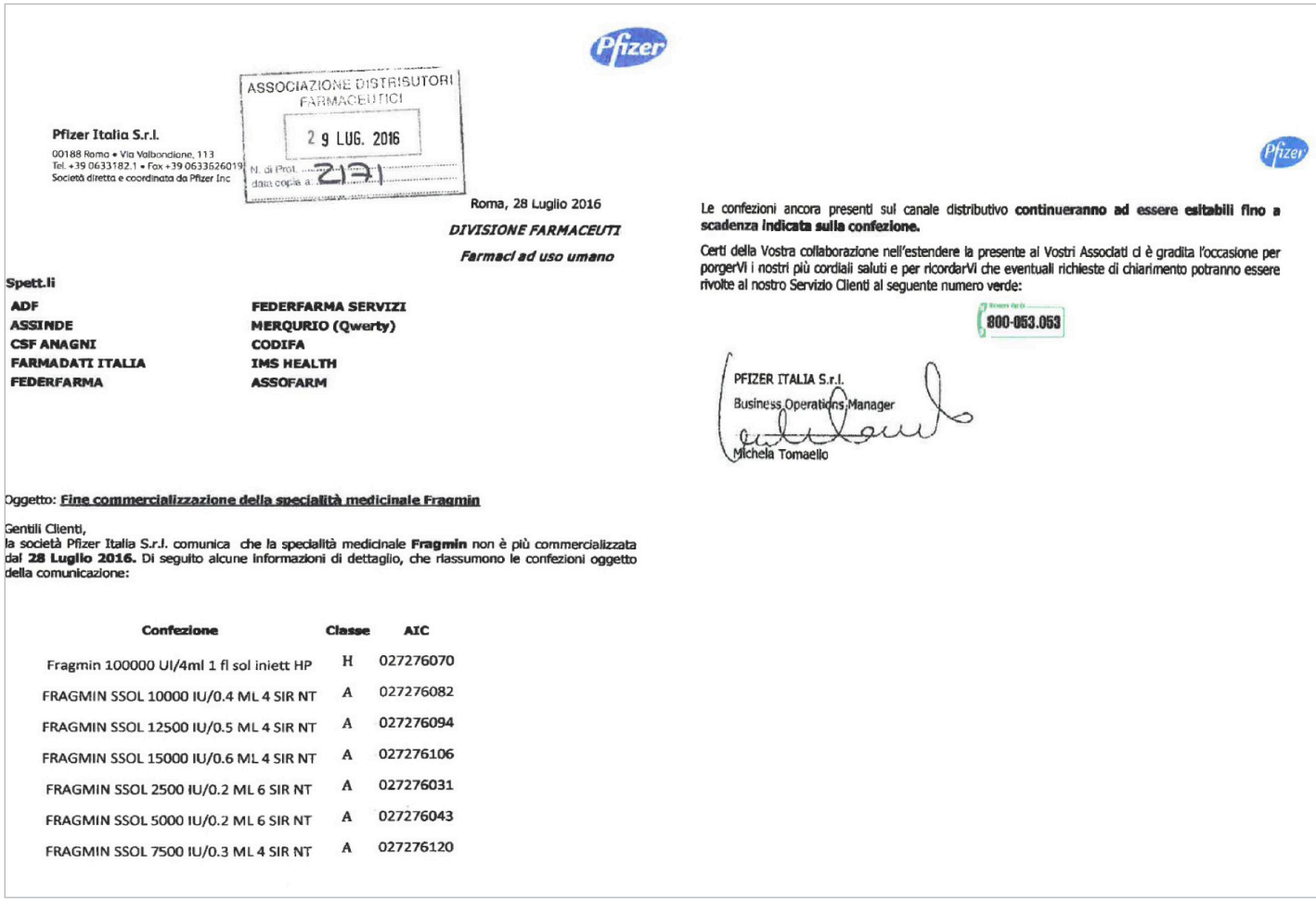


Mahè I et al Thromb Haemost 2007; 97: 581–586

The CLOT Study: Recurrent VTE



Lee, Levine, Kakkar, Rickles et.al. *N Engl J Med*, 2003;349:146



Pfizer Italia S.r.l.
00188 Roma • Via Valbondione, 113
Tel. +39 0633182.1 • Fax +39 0633626019
Società diretta e coordinata da Pfizer Inc

ASSOCIAZIONE DISTRIBUTORI FARMACEUTICI
29 LUG. 2016
N. di Prot. 2131
data copia a

Roma, 28 Luglio 2016

DIVISIONE FARMACEUTI

Farmaci ad uso umano

Spett.li

ADF	**FEDERFARMA SERVIZI**
ASSINDE	**MERQURIO (Qwerty)**
CSF ANAGNI	**CODIFA**
FARMADATI ITALIA	**IMS HEALTH**
FEDERFARMA	**ASSOFARM**

Oggetto: **Fine commercializzazione della specialità medicinale Fragmin**

Gentili Clienti,
la società Pfizer Italia S.r.l. comunica che la specialità medicinale **Fragmin** non è più commercializzata dal **28 Luglio 2016.** Di seguito alcune informazioni di dettaglio, che riassumono le confezioni oggetto della comunicazione:

Confezione	Classe	AIC
Fragmin 100000 UI/4ml 1 fl sol iniett HP	H	027276070
FRAGMIN SSOL 10000 IU/0.4 ML 4 SIR NT	A	027276082
FRAGMIN SSOL 12500 IU/0.5 ML 4 SIR NT	A	027276094
FRAGMIN SSOL 15000 IU/0.6 ML 4 SIR NT	A	027276106
FRAGMIN SSOL 2500 IU/0.2 ML 6 SIR NT	A	027276031
FRAGMIN SSOL 5000 IU/0.2 ML 6 SIR NT	A	027276043
FRAGMIN SSOL 7500 IU/0.3 ML 4 SIR NT	A	027276120

Le confezioni ancora presenti sul canale distributivo **continueranno ad essere esitabili fino a scadenza indicata sulla confezione.**

Certi della Vostra collaborazione nell'estendere la presente ai Vostri Associati ci è gradita l'occasione per porgerVi i nostri più cordiali saluti e per ricordarVi che eventuali richieste di chiarimento potranno essere rivolte al nostro Servizio Clienti al seguente numero verde:

800-053.053

PFIZER ITALIA S.r.l.
Business Operations Manager
Michela Tomaello

Le Lineeguida EMA per l'approvazione di biosimilari di EBPM

Guideline	Document Reference
CHMP Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues (revision 1)	(EMA/CHMP/BWP/247713/2012)
CHMP Guideline on Similar Biological Medicinal Products containing Biotechnology-Derived Proteins as Active Substance: Non-Clinical and Clinical Issues	(EMEA/CHMP/42832/05)
Guideline on Non-Clinical and Clinical Development of Similar Biological Medicinal Products containing Low-Molecular-Weight-Heparins	(EMEA/CHMP/BMWP/118264/2007)
Concept paper on the revision of the guideline on nonclinical and clinical development of similar biological medicinal products containing low molecular-weight heparins	EMA/CHMP/BMWP/522386/2011

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

21 July 2016
EMA/CHMP/482423/2016
Committee for Medicinal Products for Human Use (CHMP)

Summary of opinion[1] (initial authorisation)

Inhixa
enoxaparin sodium

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

21 July 2016
EMA/CHMP/482415/2016
Committee for Medicinal Products for Human Use (CHMP)

Summary of opinion[1] (initial authorisation)

Thorinane
enoxaparin sodium

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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

UNICA DOCUMENTAZIONE CLINICA SU EFFICACIA E SICUREZZA: STUDIO RANDOMIZZATO SU 20 VOLONTARI SANI, SINGOLO CIECO, CROSS-OVER

International non-proprietary name: enoxaparin sodium

Procedure No. EMEA/H/C/004264/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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

Draft agreed by Biosimilar Medicinal Products Working Party (BMWP)	April 2008
Adopted by CHMP for release for consultation	April 2008
End of consultation (deadline for comments)	October 2008
Draft agreed by BMWP	February 2009
Adopted by CHMP	October 2009
Draft revision agreed by BMWP	November 2012
Adopted by CHMP for release for consultation	17 January 2013
Start of public consultation	31 January 2013
End of consultation (deadline for comments)	31 July 2013
Agreed by BMWP	October 2016
Adopted by CHMP	10 November 2016
Date of coming into effect	01 June 2017

This guideline replaces 'Guideline on non-clinical and clinical development of similar biological medicinal products containing low-molecular-weight-heparins' (EMEA/CHMP/BMWP/118264/2007).

CONCLUSIONI

Due copie di EBPM enoxaparina sono state approvate da EMA.

Si tratta del primo farmaco biosimilare approvato in Europa senza uno studio clinico di efficacia e sicurezza eseguito su pazienti.

La procedura di approvazione seguita è in difformità con le lineeguida EMA tuttora in corso di validità e con le raccomandazioni ISTH sulla materia.

Il contenimento dei costi in sanità è un fine nobile ed ineludibile ma va sempre improntato alla massima trasparenza. il caso delle EBPM biosimilari rappresenta un inquietante precedente.