The regulation of heparin medicinal products in EU

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Dichiarazione di trasparenza/interessi*

Le opinioni espresse in questa presentazione sono personali e non impegnano in alcun modo l'AIFA

Interessi nell'industria farmaceutica	NO	Attualmente	Da 0 a 3 anni precedenti	oltre 3 anni precedenti
INTERESSI DIRETTI:				
1.1 Impiego per una società: Ruolo esecutivo in una società farmaceutica	X	☐	☐	☐ obbligatorio
1.2 Impiego per una società: Ruolo guida nello sviluppo di un prodotto farmaceutico	X	☐	☐	☐ obbligatorio
1.3 Impiego per una società: altre attività	X	☐	☐	☐ facoltativo
2. Consulenza per una società	X	☐	☐	☐ facoltativo
3. Consulente strategico per una società	X	☐	☐	☐ facoltativo
4. Interessi finanziari	X	☐	☐	☐ facoltativo
5. Titolarità di un brevetto	X	☐	☐	☐ facoltativo
INTERESSI INDIRETTI:				
6. Sperimentatore principale	X	☐	☐	☐ facoltativo
7. Sperimentatore	X	☐	☐	☐ facoltativo
8. Sovvenzioni o altri fondi finanziari	X	☐	☐	☐ facoltativo
9. Interessi Familiari	X	☐	☐	☐ facoltativo

* Lorenzo Montrasio, secondo il regolamento sul Conflitto di Interessi approvato dal CdA AIFA in data 25.03.2015 e pubblicato sulla Gazzetta Ufficiale del 15.05.2015 in accordo con la policy EMA /626261/2014 sulla gestione del conflitto di interessi dei membri dei Comitati Scientifici e degli esperti.

N.B. <Per questo intervento non ricevo alcun compenso>

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Type of regulatory procedures for marketing authorization in EU

National (Directive 2001/83/EC)

Mutual Recononition (Directive 2001/83/CE)

Decentralised (Directive 2001/83/CE)

Centralised Regulation Regulation (EC) No 726/2004

Biological products

A biological medicinal product is a product, the active substance of which is a biological substance. A biological substance is a substance that is produced by or extracted from a biological source and that needs for its characterisation and the determination of its quality a combination of physico-chemical-biological testing, together with the production process and its control.

Heparin(s) are considered as biological active substances/medicinal products

Extracted from a biological source

Physico-chemical-biological testing for characterisation

The quality is defined by its physico-chemical and biological characteristics as well as its manufacturing process

The Marketing Authorisation

The MA Holder should have full access to manufacturing data (ASMF procedure is not applicable)

Starting materials, intermediates and reagents should be adequately describes

Variability in sourcing and/or initial manufacturing steps is allowed if detailed described and justified

Definition of ‘starting materials’ for the active substance manufacturing should be unique (between regulators and industry).

The Marketing Authorisation

Sourse: supplier of intermediate or starting material (one source could include multiple slaughterhouses under the same QS).

Starting material: pooled porcine intestinal mucosae

Intermediate: substance produced during the manufacturing process before the active substance

Any other substances are defined as raw materials

Some aspects with potential impact on quality and safety

EMA/CHMP/BWP/429241/2013 (London, 27 June 2013)

Species and country of origin

Traceability from slaughterhouses/abattoirs

Prevention of species cross contamination

Animals used should fit for human consumption

Veterinary certification

Variant manufacturing processes within the same MA (different sourses)

Some flexibility within the concept of a single manufacturing process

Variant should be well defined, listed, described and justified in the MA dossier for each intermediate

Focus on critical quality attributes and critical process parameters, traceability and MAH oversight

Qualified Person's declaration concerning GMP compliance of the DS manufacture

Name and address of each manufacturing site involved in the manufacture of the active substance, beginning from the first use of the starting material.

Manufacturing operation / activity of each site

The declaration is made by the QP responsible for GMP compliance of the active substance on behalf of all the involved QPs named on the relevant MIAH(s)

EU Biosimilar approach
(Legal basis)

Article 6 of Regulation (EC) No 726/2004

Article 10(4) of Directive 2001/83/EC

Dossier requirements: Part II, Section 4 of the Annex I of Directive 2001/83/EC

Comprehensive comparability exercise applicable to any biological medicinal product

Quality characteristics

Biological activity

Safety and Efficacy

Demonstration of the similar nature of the concerned products and knowledge on how to interpret any differences.

Biosimilar

Highly purified products

Same posology and route of administration

Improve efficacy is out of the scope

Advantage in safety should be addressed

Extrapolation of indications scientifically justified

Identification of brand name and batch number

Reference Product

A single medicinal product authorised in the EEA (Article 8 of Directive 2001/83/EC)

Non-EEA authorised for certain clinical studies and in in vivo non-clinical studies

Bridging data between the proposed biosimilar, the EEA-authorised reference product and the non EEA-authorised comparator

Stepwise approach

Starting from physicochemical and biological characterisation

Extent and nature of non-clinical *in vivo* studies and clinical studies depending on evidence obtained in previous steps

Studies should detect differences (design, conduct, endpoints and/or population)

Similar biological medicinal products containing LMWH

Guideline on non-clinical and clinical requirements for comparative clinical trial

High heterogeneity

Structure-effect relationship not fully elucidated

PD markers anti-FXa and anti-FIIa activity not fully reflect/predict efficacy

EMEA/CHMP/BMWP/118264/2007 Rev. 1

2010 US FDA ANDA procedure (”generic” enoxaparin)

Bioequivalent

Same active ingredient

Route of administration

Dosage form, strength

Previously approved conditions of use

No clinical safety or efficacy data

FDA 5 criteria (+1)

1. Equivalence of physicochemical properties
2. Equivalence of heparin source material and mode of depolymerization
3. Equivalence of disaccharide building blocks, fragment mapping and sequence of oligosaccharide species
4. Equivalence in biological and biochemical assays
5. Equivalence of in vivo pharmacodynamic profile

+ 1 Characterisation of the interaction of enoxaparin for PF4

EU: reduction in clinical data requirements could, in exceptional cases, be possible?

Extent of variation in the data between test and reference product

Analytical methods

How many orthogonal analytical methodologies

Conclusion

Product Lifecycle key issues:

Comparability for biosimilar, new applications and already authorized products (variations for dossier update and new manufacturing sites)

Overall responsibilities of MAH (deep knowledge of traceability, process and product)

Need for harmonization (quality of dossier documentation, assessment approach in compliance with updated GLs): worksharing regulatory procedures