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*Short communication*

# Evaluation of commercially available low molecular mass heparin products: an internal market surveillance study

Ina Baručija[1], Amar Elezović[1], Alija Uzunović[1], Sabina Bešlagić[2], Dženita Softić[1]

[1]*Control laboratory, Agency for Medicinal Products and Medical Devices of Bosnia and Herzegovina, Sarajevo, Bosnia and Herzegovina*
[2]*Agency for Medicinal Products and Medical Devices of Bosnia and Herzegovina, Banja Luka, Bosnia and Herzegovina*

## Introduction

Low molecular mass heparins (LMWHs) are widely used anticoagulant medicines with a complex heterogeneous structure and well-defined pharmacopoeial activity profile. Despite having the same international non-proprietary name (INN), commercially available products may differ depending on manufacturer, production process, and dosage strength (Ye et al., 2013).

The importance of strict quality control of heparin-based products was particularly emphasized after the global heparin contamination crisis in 2007–2008, when oversulfated chondroitin sulfate (OSCS), a structurally similar contaminant, entered the supply chain and caused severe adverse reactions and fatalities worldwide. The incident demonstrated limitations of outdated analytical testing methods and highlighted the need for continuous modernization of pharmacopoeial standards and post-marketing surveillance (Usdin, 2009).

Market surveillance studies represent a post-marketing quality control approach that enables evaluation of pharmaceutical products as they are available in real-world clinical use. Unlike pre-approval testing, internal surveillance studies provide insight into actual market variability and compliance with pharmacopoeial specifications.

In the case of LMWHs, biological activity is characterized by anti-factor Xa and anti-factor IIa activities, and their ratio represents a critical quality attribute for product characterization according to the European Pharmacopoeia

In response to the contamination crisis, regulatory authorities introduced additional analytical approaches for characterization and quality assurance of heparin and LMWH products, including one-dimensional proton nuclear magnetic resonance spectroscopy (1D $^1$H NMR), strong-anion-exchange high-performance liquid chromatography (SAX-HPLC), capillary electrophoresis (CE), and chromogenic anti-factor Xa and anti-factor IIa activity assays. These complementary methods provide improved detection of impurities, contaminants, and variability between products from different manufacturers. (Ye et al., 2013).

## Materials and methods

An internal market surveillance study was conducted on 22 commercially available low molecular mass heparin (LMWH) samples collected from the market. Products from different manufacturers and dosage strengths (IU/mL) were included in the study.

*i.barucija@almbih.gov.ba

Anti-factor Xa and anti-factor IIa activities were determined according to the European Pharmacopoeia using validated chromogenic substrate assays. Each activity was measured individually for all samples under standardized laboratory conditions.

Heparin inhibits factor Xa or factor IIa activity, and the residual enzymatic activity is measured using a chromogenic substrate. A coloured product is formed during the reaction and measured spectrophotometrically. Lower colour intensity indicates higher anticoagulant activity of heparin.

The anti-Xa/anti-IIa ratio was calculated for each sample as a characteristic pharmacopoeial quality parameter for LMWH classification and comparison among different products.

In addition to activity testing, selected quality parameters were evaluated, including bacterial endotoxins testing, sterility testing, and pH determination.

## Results and discussion

A total of 22 LMWH samples from different manufacturers and dosage strengths were included in the study. All tested samples were evaluated in accordance with the European Pharmacopoeia requirements for LMWH biological activity. The anti-Xa/anti-IIa ratio showed characteristic LMWH profiles, confirming the expected pharmacological pattern for this class of anticoagulants.

Analytical evaluation demonstrated variability in anti-Xa and anti-IIa activities between products, reflecting differences in manufacturing processes and formulation strengths.

No atypical activity profiles or deviations that suggest contamination were detected. The obtained findings support previous reports emphasizing the importance of modern analytical methodologies for quality assurance of complex biological medicines (Ye et al., 2013).

The results additionally confirm the significance of continuous post-marketing monitoring of LMWH products, particularly considering historical contamination events that revealed vulnerabilities in global pharmaceutical supply chains (Usdin, 2009).

## Conclusion

Market surveillance studies that include pharmacopoeial anti-Xa and anti-IIa activity testing represent a reliable approach for post-marketing quality assessment of LMWH products. The anti-Xa/anti-IIa ratio is a critical quality parameter for characterization and comparison of commercially available LMWHs.

Regular surveillance studies contribute to monitoring of real-world variability among manufacturers and support continuous assurance of pharmaceutical quality and compliance with European Pharmacopoeia requirements.

## References

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