

# Qualitätssicherung von Arzneimitteln am Beispiel Heparin

Andreas Mayrhofer  
OMCL

AGES PharmMed-Tag  
Wien, 12.05.2010

# Inhalt



1. Einleitung
2. Heparinmarktüberwachung durch das OMCL
3. OMCL-Mitarbeit bei der Revision der Heparin-Monographien
  - 1. Rapid Revision
  - 2. Rapid Revision
4. Conclusio

# Introduction

## “Death by contaminated Heparin”



- **03 March 08:** 1st Infos about OSCS from ILFCM/FDA
- **11 March 08:** Discussion in Ph.Eur. Comm.
  - Revision of monograph
  - AT: MSS Heparin startet, all APIs + parenterals
  - OMCL Network: exchange of results (EDQM)
- **9 April 08:** NMR/CE test order to companies
- **11 April 08:** LM Heparins may be contaminated
  - AT: MSS LM Heparins startet, all APIs + parenterals
- **23 April 08:** OSCS → → Anaphylatoxin  
*(New Engl. J. Med., preprint)*



# Chinese Heparin Export Statistics 2007



## HEPARIN

Region	%	Country/EU	%
<b>Europe</b>	<b>68.5</b>	DE	22.9
N-America	21.7	FR	17.7
Asia	8.0	IT	13.7
S-America	1.4	<b>AT</b>	<b>8.5</b>

## LM - HEPARIN

Region	%
Asia	87.3
<b>Europe</b>	<b>2.2</b>



# Complete Surveillance of Heparins March – August 2008

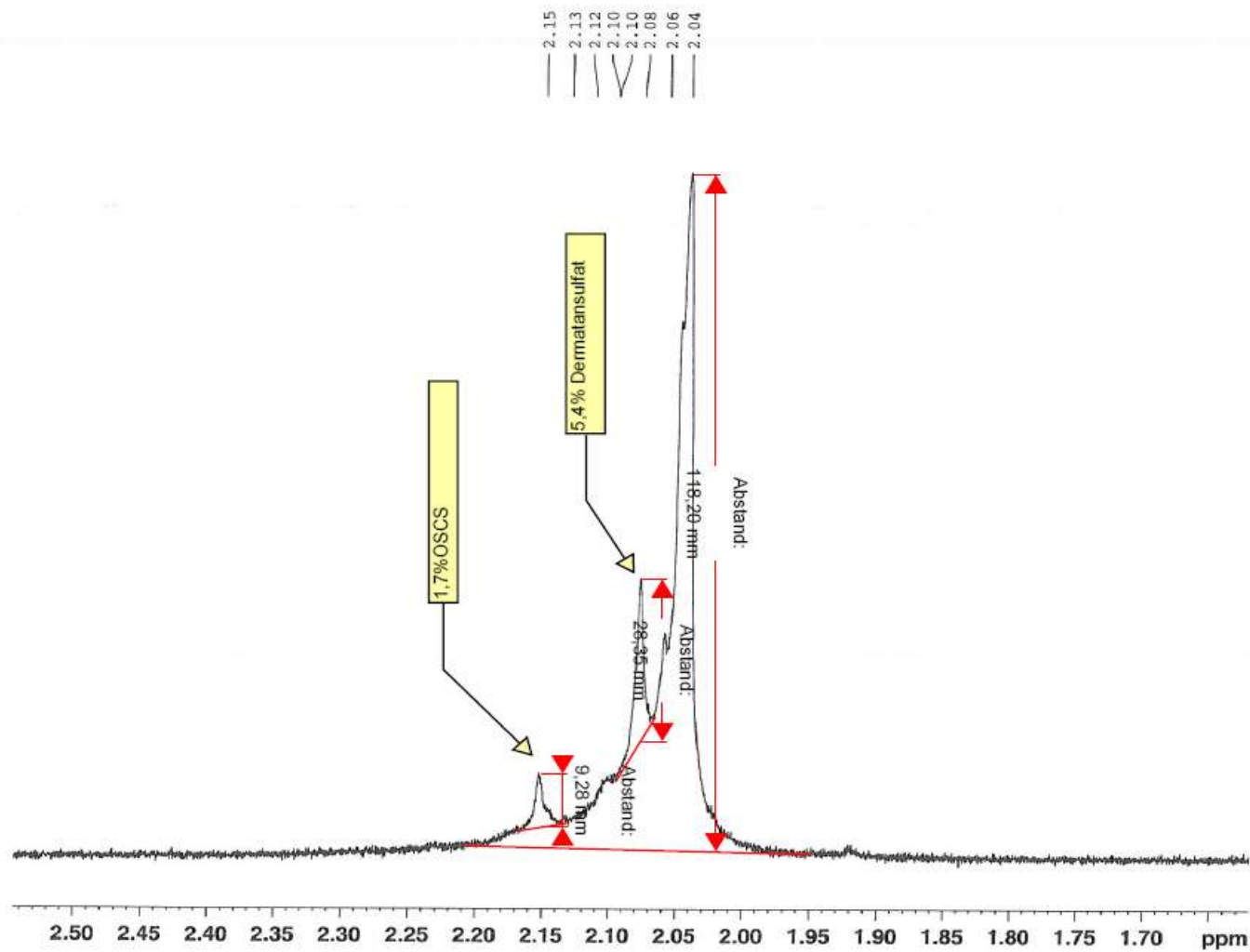


## Analytical Methods

- $^1\text{H}$ -NMR (500 MHz)
  - **Limits AT: OSCS max. 1.0%, DS max. 5.0%**
  - Quantitation by N-ac. peak height ratio
  - Validation with OSCS + DS standards
  - Isolation from finished products
    - Ethanol precipitation or evaporation
- Ph.Eur. tests
  - Stopped after 42 samples (no trend)
- Electrophoresis on cellulose acetate
  - For cross validation (needs heparin digest)

# Analytical Methods

## <sup>1</sup>H-NMR



# Analytical Methods

## Electrophoresis



CS

DS

OSCS

### Standard Series: OSCS+CS+DS

1. Sample: 7.9% OSCS
2. 0.4%
3. 0.5%
4. 1%
5. 2%
6. 3%
7. 4%
8. 5%

# Complete Surveillance of Heparins March – August 2008



## Results

- Sampling + Testing of all products on market
  - 193 samples (incl. APIs)
    - **3 FDF batches exchanged: 1.1 – 2.3% OSCS**
- Temporary batch release
  - 268 batches: assessment of **NMR** (scanned + integrated) + CE
    - **4 rejected**

# Revision of Heparin Monographs



- **1<sup>st</sup> Rapid Revision**

- Adopted in Ph.Eur.COM: June 2008
- Rapid Implementation: 1 August 2008
- **New Production Section:**

- ✓ **NMR**

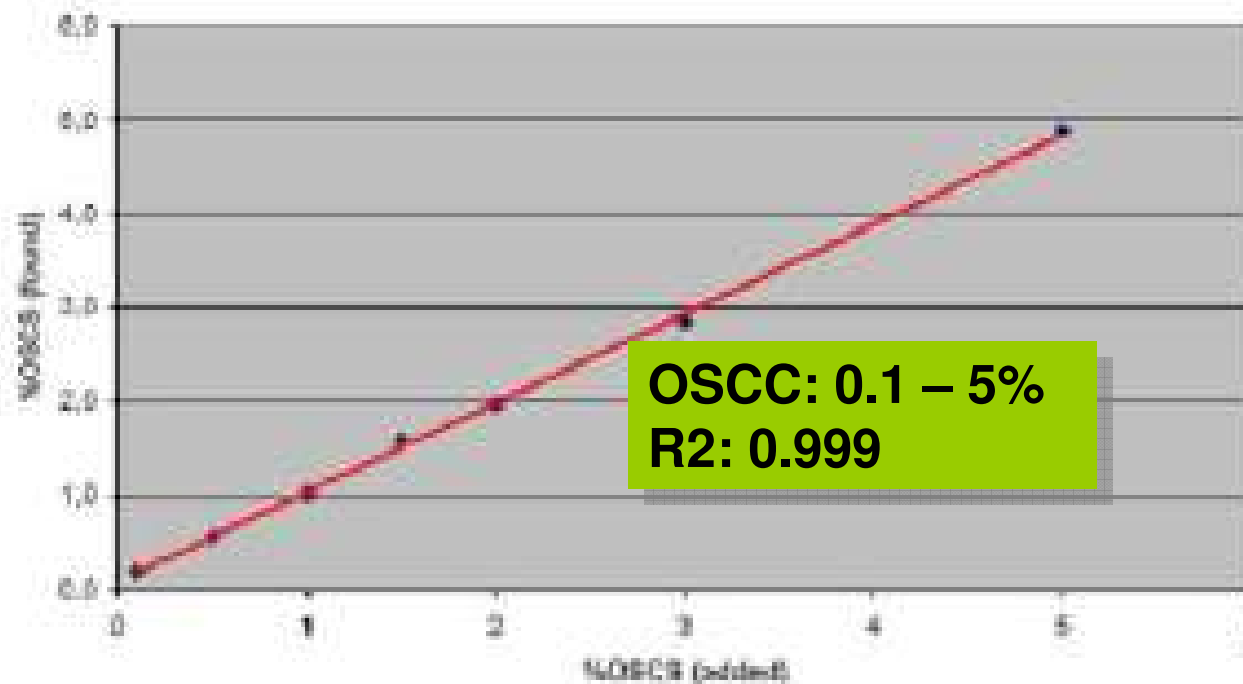
- ✓ **CE**

*complies spec. approved by authority*

# Revision of Heparin Monographs



- **Ad hoc Exp. Gr. on Heparin** (start 16 Sept. 2008)
  - AT, DE, PL, SE, UK
  - EDQM standard method for completion of 1<sup>st</sup> revision
  - Collaborative Study for validation and tightening OSCS limit



# Revision of Heparin Monographs



## Pharmeuropa Bio 2008-1 (Dec.)

<sup>1</sup>H-NMR for Oversulphated Chondroitin Sulphate and Dermatan Sulphate in Heparin

---

### Determination of Oversulphated Chondroitin Sulphate and Dermatan Sulphate in unfractionated Heparin by <sup>1</sup>H-NMR

Collaborative Study for Quantification and Analytical Determination of LoD

I. McEwen, B. Mulloy, E. Hellwig, L. Kozerski, T. Beyer, U. Holzgrabe, A. Rodomonte, R. Wanko, J-M. Spieser

#### ABSTRACT

*Oversulphated Chondroitin Sulphate (OSCS) and Dermatan Sulphate (DS) in unfractionated heparins can be identified by nuclear magnetic resonance spectrometry (NMR). The limit of detection (LoD) of OSCS is 0.1% relative to the heparin content. This LoD is obtained at a signal-to-noise ratio (S/N) of 2000:1 of the heparin methyl signal. Quantification is best obtained by comparing peak heights of the OSCS and heparin methyl signals. Reproducibility of less than 10% relative standard deviation (RSD) has been obtained. The accuracy of quantification was good.*

# Revision of Heparin Monographs



## • 2<sup>nd</sup> Rapid Revision

- Adopted in Ph.Eur.COM: March 2010
- Rapid Implementation: 1 August 2010

### Complete Monograph revised:

- ✓ Definition: min. **180 IU/mg** (presently 150)
- ✓ Identification
  - ✓ Opt. rotation + zone electrophoresis replaced
  - ✓ **NMR: alerts to possible contaminants**
  - ✓ **SAX-HPLC**
  - ✓ Sodium: AAS

# Revision of Heparin Monographs



## • 2<sup>nd</sup> Rapid Revision

### ✓ Tests

- ✓ Nucleotidic impurities: limit tightened
- ✓ Protein: Lowry test replaces absorbance
- ✓ **Related substances: SAX-HPLC** after heparin digest
  - ✓  $\Sigma$  **DS** + chondroitin sulfate: max. **2.0%** (harmonized with USP)
  - ✓ **OSCS neg.** („no other peaks“)
- ✓ Nitrogen: 1.5 – 2.5% (presently n.m.t. 2.5%)
- ✓ Heavy metals: method F (acid digest instead ignition)
- ✓ Sulfated ash: deleted

# Conclusio



- **Aufwand gerechtfertigt??**

- Temporäre totale Marktüberwachung + "Monographie-Verteuerung"

- **Stand der Wissenschaften richtig interpretiert??**

- OSCS max. 1% (Eur.: 0 – 3%)

- **JA, WEIL.....**


- Wahre Todesfallzahl unbekannt + ↑ (*Worldfocus Dez. 08*)

- **Todesfälle: ca. 150 → 1000**
- Schwere Zwischenfälle: Tausende
- Ab 6% OSCS-Kontamination toxisch

- Bisher größte AM-Fälschung in legaler Verteilerkette

# Conclusio



- **Patente sind eine Goldmine für AM-Fälscher**
  - **OSCS als synthetisches Heparinoid entwickelt** (99% billiger)
  - Mäusetest verlief letal → nicht publiziert
  - **Chinesische AM-Fälscher synthetisierten OSCS (Dez. 2005) und „testeten“ die Qualitätskontrollsysteme in USA + Eur.**
  - Heparin-Monographien im Kern 80J. alt
    - Kein chromatographischer Test
  - Nur 1 Fa. kam fast drauf (Sandoz - Tirol)
    - Zus. unbekannte Imp. im Elektrophorese-Test auf DS ⇒ 
- **Heparin- u. Melamin-Skandal sind vergleichbar**
- **Keine Heparin-OSCS-Zwischenfälle in AT**

# Danke



- Auditorium
- Egon Hellwig
- Martina Waismayer
- Uni Wien – Pharmaziezentrum (NMR)

