Heparin Case Study

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Securing Medical Product Quality Through the Supply Chain
USP
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Agenda

• Heparin Primer/History
• Supply Chain Characteristics
• Economically-Motivated Adulteration
• Blue Ear Disease
• OSCS
• What Happened
• FDA and USP Response
• Import Alert 55-03 and FDA Guidance
• Questions
Primer

• Heparin is a widely-used anticoagulant
• Used as a drug and incorporated in devices
• Derived naturally from porcine (pig) intestines
• Is a polymer, and variants exists (low vs. high molecular weights)
Heparin History

Supply Chain Characteristics

• It takes many animals to produce the heparin supply
  – ~3000 pigs for 1 kg of heparin
• The supply chain spreads back to slaughterhouses, crude manufacturers, and consolidators
• The supply chain is intertwined; it is an older industry with multiple manufacturers
The Heparin Supply Chain
General Crude Heparin Supply Chain (China) Risks/Traceability

- Slaughter Houses: >25,000 (2 millions Kills/day)
- Casting Workshops >1,000. Buy pigs Intestines. Daily processing 1,000-20,000 kg intestines.
- Mucosa Crude: 15-300 kg/month.
- Consolidators: Dozens. Mix crude daily output. Dissolve. Precip. Dry. Multiple tests 300-2,000 kg/month. Some consolidators are also heparin pharma companies.

Domestic Pharma buyers
Foreign buyers
Global distributions of pigs

With estimated standing populations of 1.43 billion cattle, 1.87 billion sheep and goats, 0.98 billion pigs and 19.60 billion chickens.


http://journals.plos.org/plosone/article?id=info:doi/10.1371/journal.pone.0096084
Economically Motivated Adulteration (EMA)
Working Definition of EMA

“For purposes of this public meeting, FDA proposes a working definition of EMA as the fraudulent, intentional substitution or addition of a substance in a product for the purpose of increasing the apparent value of the product or reducing the cost of its production, i.e., for economic gain. EMA includes dilution of products with increased quantities of an already present substance (e.g., increasing inactive ingredients of a drug with a resulting reduction in strength of the finished product, or watering down of juice) to the extent that such dilution poses a known or possible health risk to consumers, as well as the addition or substitution of substances in order to mask dilution.”

Federal Register /Vol. 74, No. 64 /Monday, April 6, 2009 /Notices
Department of Health And Human Services/Food and Drug Administration
[Docket No. FDA–2009–N–0166]

https://www.fda.gov/NewsEvents/MeetingsConferencesWorkshops/ucm163619.htm
Econ 101

**KEY**: The interaction of *supply* and *demand* determines the optimal *PRICE* and *QUANTITY DEMANDED* (aka *Equilibrium* $P$ and $Q$).

**FALL IN SUPPLY**

1. $\uparrow P_R$ Price of related good
2. $\uparrow C$ Cost of production
3. Unfavourable unplanned factors (i.e. severe growing conditions for crops)

Blue Ear Disease
Blue Ear Disease

Fatal virus that affected the pig supply in China

*From the Washington Post, 9/16/2007:*

“Moving rapidly from one farm to the next, the virus has been devastating pig communities throughout China for more than a year, wiping out entire herds, driving pork prices up nearly 87% in a year and helping push the country's inflation rate to its highest levels since 1996. The Chinese government has admitted that the swine deaths amount to an epidemic…”

Effects of Blue Ear Disease

- Supply of raw material drops
- Demand for heparin stays the same
- Econ 101—price increases
- Higher price = Higher incentive for EMA
- Enter over-sulfated chondroitin sulfate (OSCS)
OSCS
Crude Heparin Pricing

Crude heparin comes in various grades
  – Depends on stage of purification
  – Form transported (resin/powder/liquid)
  – Sophistication of crude operations
  – Whether brokers/middlemen consolidate

Therefore price is a function of purity/potency
  – $ = weight X potency
  – Potency confirmed via various tests

2 Options for EMA
  – Increase the apparent potency => increased price
  – A cheaper material with similar potency test results => reduce your cost
Heparin vs OSCS

Chondroitin Sulfate

Heparin

http://web.mit.edu/newsoffice/2008/heparin-1203.html
“OSCS is not a natural product arising from animal sources. Therefore, it must be concluded that this was not a case of accidental contamination, but that OSCS was intentionally added to the raw heparin product as an act of purposeful adulteration.”

“The high charge density of OSCS resulted in strong anti-factor IIa activity, allowing the contaminated sample lots to pass through the anticoagulation potency screens that were used to determine heparin efficacy and purity.”

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3015169/
### Table 2: Effect of OSCS on activity of unfractionated heparin

<table>
<thead>
<tr>
<th>Assay type</th>
<th>IU/mg (95% confidence limits)</th>
<th>Heparin + 15% OSCS</th>
</tr>
</thead>
<tbody>
<tr>
<td>EP Sheep Plasma</td>
<td>165.9 (160.4–171.4)</td>
<td>200.1 (193.7–206.5)</td>
</tr>
<tr>
<td>Anti-Xa</td>
<td>172.8 (169.1–176.5)</td>
<td>177.5 (173.7–181.3)</td>
</tr>
<tr>
<td>Anti-IIa</td>
<td>168.4 (154.4–182.4)</td>
<td>179.0 (162.9–186.1)</td>
</tr>
</tbody>
</table>

Rebecca Lever, Barbara Mulloy, Clive P. Page
*Heparin – A Century of Progress*, ISBN 978-3-642-23055-4
What happened?
A Perfect Storm

• Opaque supply chain
  – Many didn’t know who crude manufacturers were (bought material from brokers/consolidators)
  – Comingled materials hinder traceability

• Crude material with natural impurities

• Weak analytical controls
  – Only test for potency
  – Methods wouldn’t detect OSCS

• Supply disruption causing spike in price
  – Increased incentive for OSCS contamination
FDA and USP response
Advancing Health Through Public Standards
USP & FDA’s Response to Heparin Crisis: A Timeline of Events

**STAGE 1**
Official as of June 18, 2008

- **Immediate Response**
  - 2007–2008
  - March 2008
  - June 2008
  - **Crisis**
    - Heparin contamination threatens supply of safe product worldwide. Nearly 150 deaths and hundreds of serious adverse reactions reported to FDA and CDC.
  - **Collaboration**
  - **FDA**
  - **USP**
    - FDA seeks USP’s collaboration to help detect contaminated heparin.
  - **Testing**
  - **Optimizes New Methods Through**
    - Lab work
    - Selecting methods from industry
    - Validation of methods
    - Developing and validating new methods
    - Soliciting batch data records to support specifications

**STAGE 2a**

- **Development**
  - July 2008
  - Dec. 2008
  - **Test Method Validation by USP**
  - **Additional Methods from Industry**
  - **Heparin PanelFormulation**

**STAGE 2b**

- **Industry Prepares for Implementation**
  - Feb. 2009
  - March–May 2009
  - July 2009
  - **Methods Published for Comment**
  - **USP Releases 3 New Reference Standards**
  - **Industry Prepares for New Tests**
  - **Provide time for industry to prepare for new tests.**
  - **USP releases another three new Reference Standards in support of monograph written standards.**
  - **Harmonization of the USP Heparin unit with that established by the World Health Organization.**

**STAGE 3**
Began 2010

- **Ongoing**
  - Oct. 2009
  - 2010
  - **PUBLIC COMMENT**
  - **USP continues to monitor and evaluate heparin product quality.**
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Import Alert 55-03

Implemented in February 2012

- https://www.accessdata.fda.gov/cms_ia/import_alert_821.html
- Firms linked to historical OSCS contamination
- Includes firms with violative inspections (WL, etc.)
- Serves as “one stop shop” for heparin industry to be aware of firms FDA considers unacceptable
Import Alert 55-03

Pass through issue

– Material from these firms may not come across the border (internal commerce in China)

– All sponsors and API sites directly notified that use of firms on the list could result in their products being considered adulterated

– API sites committed to removing listed sites, all DMF and applications were updated accordingly
FDA Heparin Guidance

Final guidance published June 2013

*Heparin for Drug and Medical Device Use: Monitoring Crude Heparin for Quality*


Recommendations to better control crude heparin that might contain over-sulfated chondroitin sulfate (OSCS) or non-porcine material (ruminant material) contaminants
Questions?