

Introduction of Proposal for Reintroduction of Bovine Heparin to the US Market

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Science Board to the Food and Drug Administration

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Objective

- CDER is concerned about the shortage and potential contamination of porcine heparin.
- To address, future possible shortages or contamination of the global porcine heparin supply, CDER is considering the reintroduction of bovine heparin into the US market.
- CDER is seeking the FDA Science Board's input with respect to risks and benefits of this proposal.

Outline

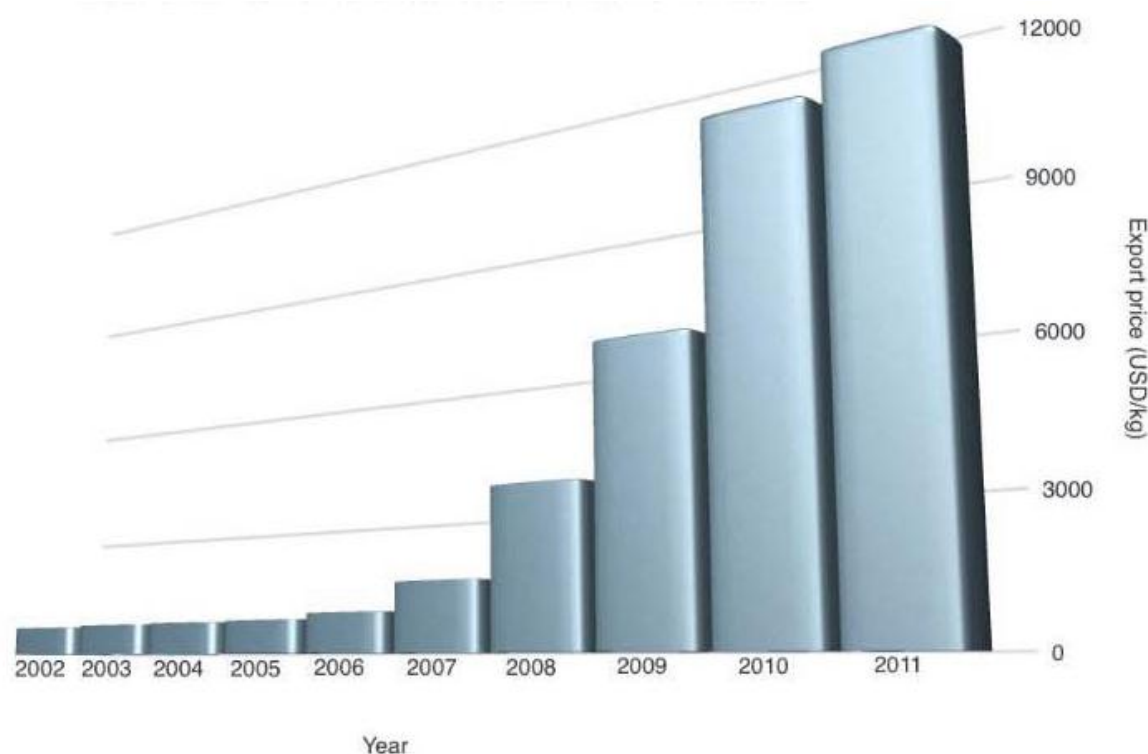
- Current status of FDA-approved porcine heparin applications
- Experience with the porcine heparin supply chain
- Regulatory history of bovine heparin New Drug Applications (NDAs)
- Current understanding of bovine spongiform encephalopathy (BSE) risk
- Questions to Science Board

FDA-approved Heparin Applications

- All heparin products currently marketed in the U.S. (NDAs, Abbreviated NDAs, and CDRH related devices) are obtained from porcine sources (intestinal mucosa).
- About 75% of the crude porcine heparin used to manufacture active pharmaceutical ingredient (API) is from outside the U.S.
 - China is the source for over half of crude heparin.
- There is little growth potential in E.U. and U.S. porcine sources.
- Without foreign supply, there could be a serious shortage of heparin in the U.S.

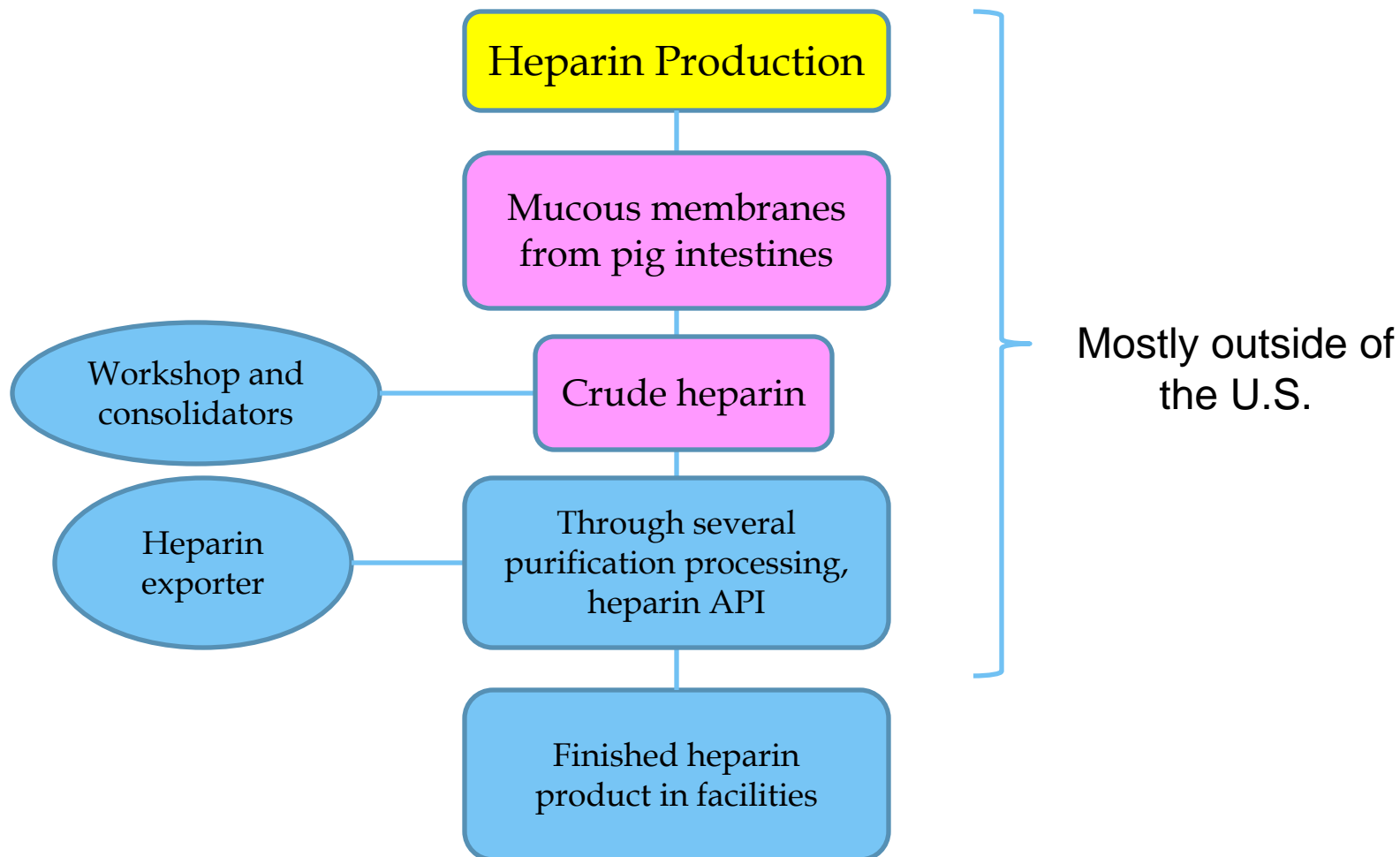
China's Crude Heparin Export Market

Price of Chinese crude heparin has tripled in recent years

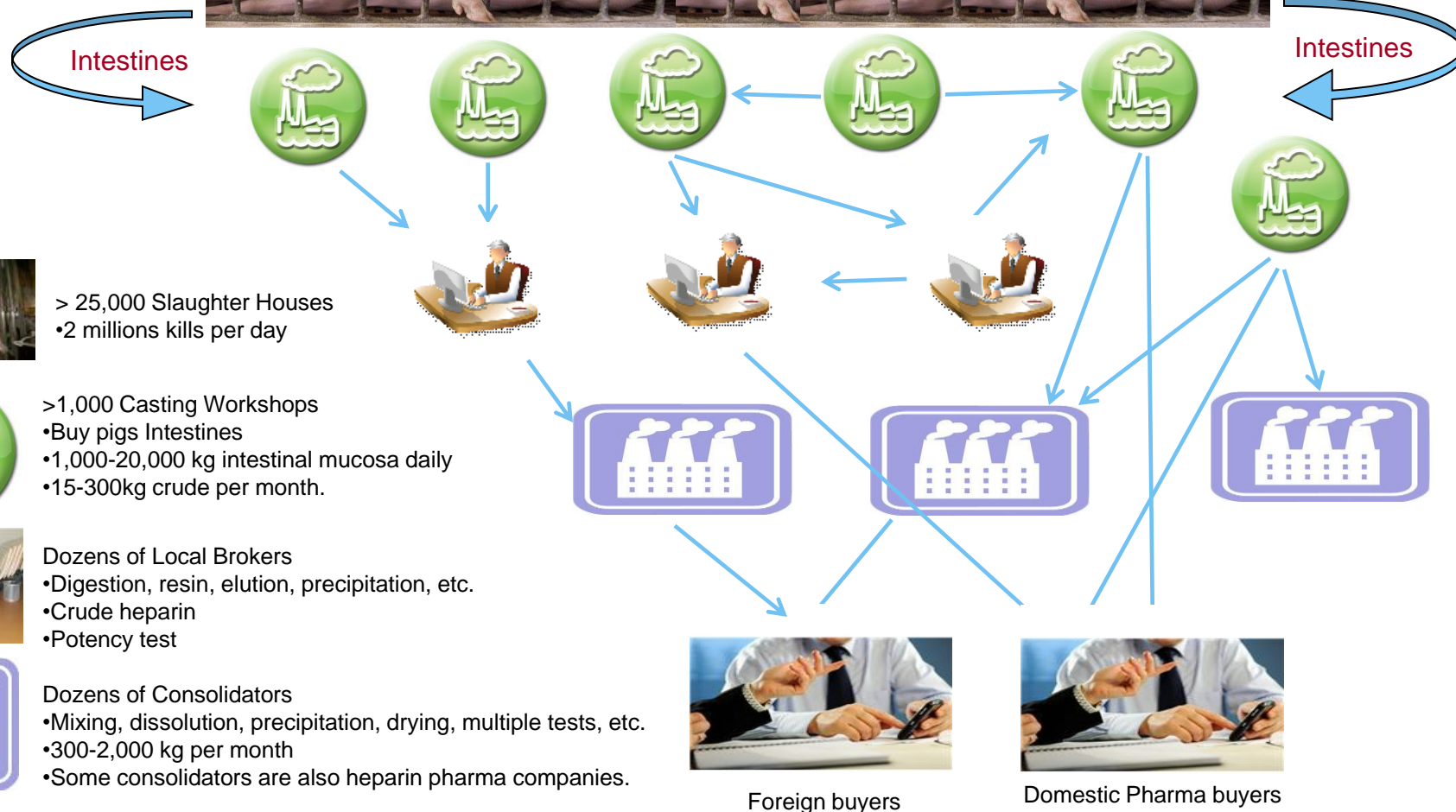


Clifford et al. China's Heparin Revisited: What Went Wrong and Has Anything Changed? Assessed May 5, 2014
<http://www.newpharmathinkers.com/wp-content/uploads/downloads/2012/08/ChinaInsider-Heparin-Revisited.pdf>

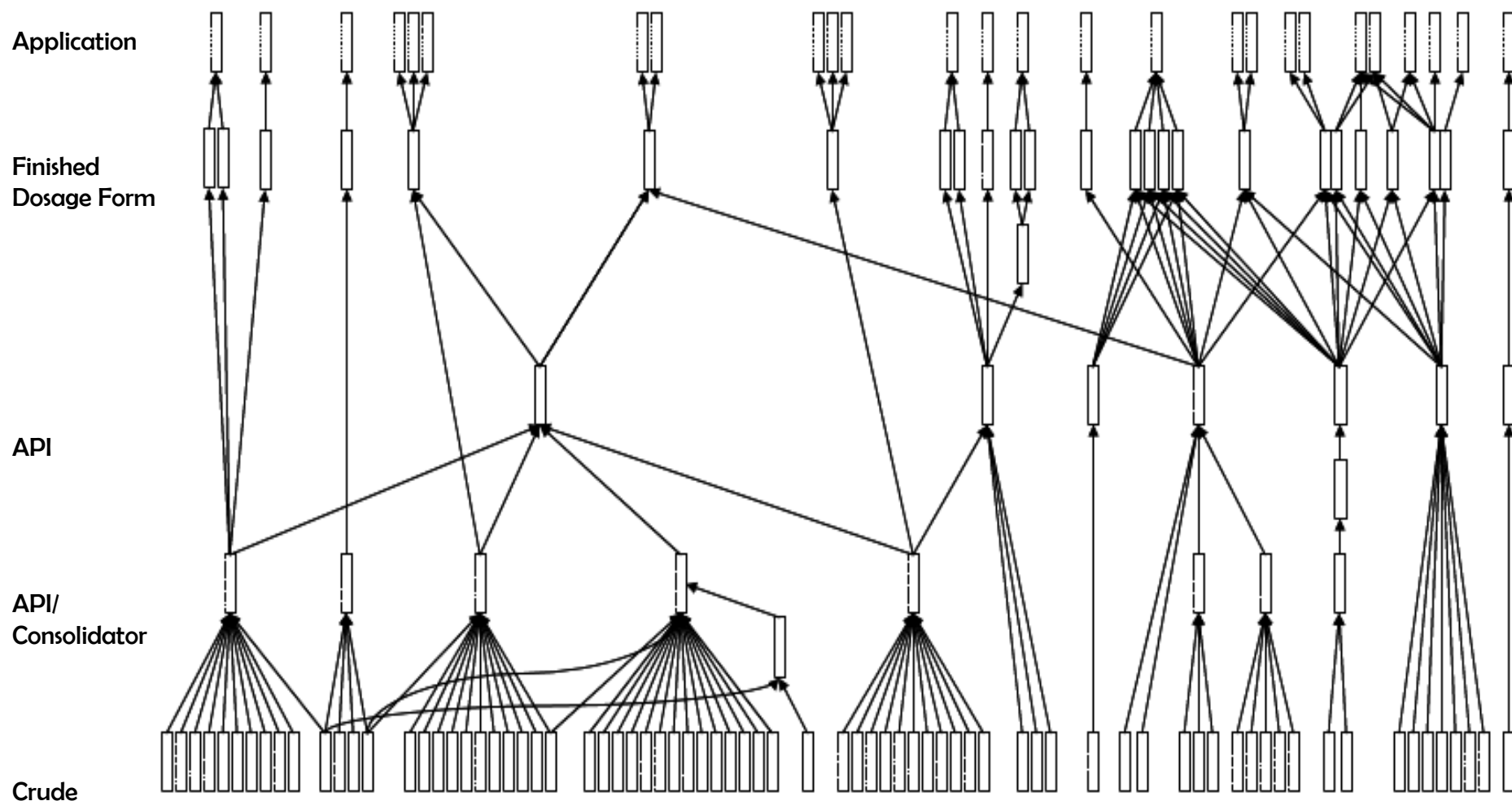
Current Porcine Heparin Manufacturing Process



Complexity of Crude Porcine Heparin Supply Chain



Porcine Heparin Supply Chain



Current Concerns for Porcine Heparin

- Shortage risk
 - Heparin is currently in shortage
 - Recent market share analysis indicates the majority of crude heparin remains to be sourced from China
 - Single animal sourcing/single country sourcing is risky due to animal-specific/country-specific risk (e.g., blue-ear disease)
- Contamination
 - Currently, the heparin supply chain is considered safe
 - Historically, heparin has been contaminated
 - Potential exists for economically motivated adulteration

Regulatory History of NDAs for Bovine Heparin

- First application approved in 1939
- Multiple applications subsequently approved
- Voluntarily removed in the 1990's from the U.S. market by the manufacturers due to concerns related to BSE.
- More than 50 years of manufacturing experience and clinical use with heparin obtained from bovine sources.

Bovine vs. Porcine Heparin:

Heparin-induced Thrombocytopenia

- Bovine heparin, like porcine heparin, is also associated with a life-threatening, immune-driven adverse event known as heparin-induced thrombocytopenia (HIT).
- A few prospective studies compared the relative risk for HIT in patients receiving either bovine (lung) or porcine (intestinal mucosa) heparin.
- The results of these studies were contradictory and inconclusive.¹
- Much of the clinical data regarding the safety and efficacy of unfractionated heparin was in fact derived from bovine heparin.

¹Ansell et al., *Chest*. 88:878-82 (1985) and Francis et al., *Ann Thorac Surg*. 75:17-22 (2003).

Bovine Spongiform Encephalopathy

- Manufacturers voluntarily removed bovine heparin products from the U.S. market in the 1990's because of concerns about possible contamination with the BSE agent.
- This did not occur in Brazil where bovine heparin¹ is currently an approved product on the market.
- The risk of BSE is now better understood.

¹It should be noted that the bovine heparin in Brazilian market is derived from bovine intestines.

CDC Report - February 21, 2013



Department of Health and Human Services

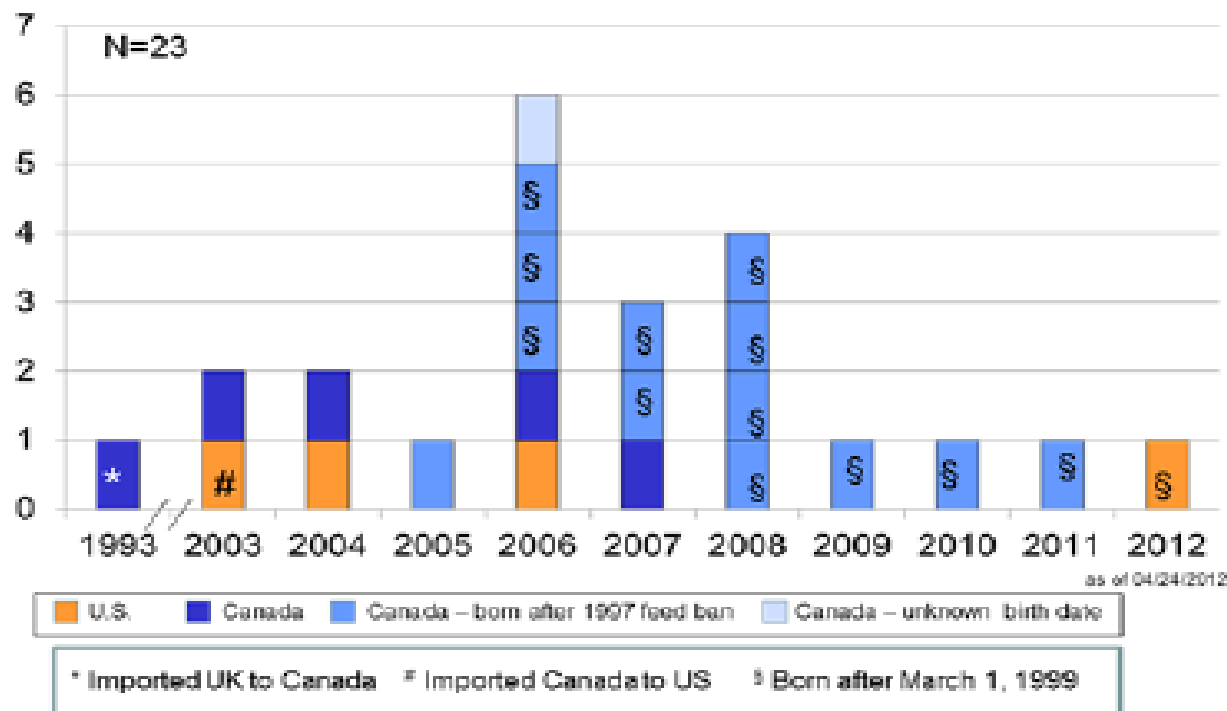
Centers for Disease Control and Prevention

BSE (Bovine Spongiform Encephalopathy, or Mad Cow Disease)

The BSE epizootic in the United Kingdom peaked in January 1993 at almost 1,000 new cases per week. Over the next 17 years, the annual numbers of BSE cases has dropped sharply; 14,562 cases in 1995, 1,443 in 2000, 225 in 2005 and 11 cases in 2010. Cumulatively, through the end of 2010, more than 184,500 cases of BSE had been confirmed in the United Kingdom alone in more than 35,000 herds.

CDC Report – February 21, 2013

BSE Cases in North America, by Year and Country of Death, 1993 - April 2012



BSE Risk Mitigation for Bovine Heparin

- It has been shown that the existing heparin manufacturing processes could have an intrinsic capability to remove or inactivate BSE agents, if present.
- The FDA has guidelines regarding TSEs that can be applied to heparin.
 - Control of animal sources, selection of types of tissue used, and incorporation of risk-reducing steps into the production process
- Development of an alternative assay for detection of BSE infectivity may overcome the significant lag time for evidence of BSE disease in traditional animal models.

Conclusion

- Heparin from bovine lung has been on the U.S. market.
- Reintroducing bovine heparin will diversify the supply chain.
- Diversifying the supply chain will be a benefit - control and mitigation of BSE contamination will be needed.

Two Presentations to Science Board

- Clinical Evidence Derived from Bovine Heparin by Ann Farrell, MD, CDER
- Understanding Risk of Iatrogenic BSE by David Asher, MD, CBER

Questions to Science Board

- What additional risk factors should the FDA consider for re-introducing bovine heparin into the US market?
- What step(s) can the FDA take to mitigate the risks associated with a foreign-sourced supply of heparin?
- What other step(s) can the FDA take to diversify the supply chain of crude heparin materials used to manufacture heparin?