UPDATE ON CDER BOVINE HEPARIN INITIATIVES

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FDA Science Board Meeting
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Recap of the June 4, 2014 Science Board Meeting on Bovine Heparin

- The Board agreed that diversifying the heparin supply chain is important to help ensure the un-interrupted supply of high quality heparin products in the US. Re-introduction of bovine heparin could be a viable option.

- The Board recommended that CDER explore utilization of a multi-step approach to minimizing the risks of bovine spongiform encephalopathy (BSE) agent contamination in bovine sourced heparin, including the assessment of:
  - Prevalence of disease within the source country;
  - Slaughterhouse practices; and
  - Capability of the heparin manufacturing processes to eliminate BSE agents (if present)
Bovine Heparin Working Group

• Office of Pharmaceutical Quality, CDER
  - Sau (Larry) Lee, Margaret Caulk, Sarah Pope Miksinski, Christine Moore, Ali Al Hakim, David Keire, Cindy Buhse, Frank Perrella, and Francis Godwin

• Office of New Drugs, CDER
  - Ann Farrell and Edvardas Kaminskas

• Office of Blood Research and Review, CBER
  - David Asher and Luisa Gregori
Source Animals

• Bovine Heparin WG is working on the BSE risk mitigation strategy with respect to control of source animals, for example:
  - Consultation with CVM and USDA
  - Criteria identified by World Organization for Animal Health (OIE) for the risk status of countries vulnerable to BSE
    • Countries or regions with a negligible BSE risk
    • Countries or regions with a controlled BSE risk
    • Countries or regions with an undetermined BSE risk
  - Tissues
    • Intestine (excluding the distal ileum) and lung are considered lower-infectivity tissues in comparison to specified risk materials (SRMs) such as the brain and spinal cord
  - Age of cattle
    • Younger animals (<30 months) have demonstrated a significant reduction of TSE agents
  - USDA-based ante- and post mortem inspection for animal health
Slaughterhouse Practices

• Bovine Heparin WG is working on the BSE risk mitigation strategy with respect to slaughterhouse practices to avoid cross-contamination with specified risk materials (SRMs), for example:
  - Consultation with CVM and USDA
  - Methods and controls of cattle slaughter
  - Removal, segregation, and disposal of SRMs
  - Equipment cleaning
  - Traceability
Process Capability to Reduce BSE Risk

- Bovine Heparin WG is investigating the capability of heparin manufacturing process to reduce BSE infectivity
  - A bench-scale manufacturing process for crude bovine heparin to produce a pure bovine heparin product has been developed for testing purposes.
  - The bench scale process steps have been tested with crude porcine heparin spiked with sheep TSE agent (BSL-2 laboratory). Animal bioassay infectivity tests are in progress.
  - Next the process steps will be applied to crude bovine heparin spiked with BSE agent (BSL-3 laboratory).
  - Spiked BSE agent removal will be tested by (a) measuring the recovery of abnormal prion protein, PrP^{TSE}, as surrogate of BSE infectivity using the in vitro RT-QuIC, and (b) the recovery of BSE infectivity using an animal bioassay.
    - The RT-QuIC method takes 2 to 3 days instead of up to 2 years for the animal bioassay. This study may validate the use of RT-QuIC for BSE infectivity risk assessment.
  - Review existing validation methods of TSE clearance
Other FDA Activities

• Analysis of global distribution of pigs and cattle that are available for heparin production
• Meeting with stakeholders
• Analytical characterization of bovine heparin structure and composition.
• Development of animal models to assess heparin induced thrombocytopenia (HIT) risk.
• Work with USP to develop a monograph for bovine heparin.