Safeguarding the global heparin supply chain: Bovine Heparin Initiative

David Keire

Laboratory Chief (Acting) Branch 1

United States Food and Drug Administration

CDER/OPQ/OTR/DPA

11/15/2016

This presentation reflects the views of the author and should not be construed to represent FDA's views or policies

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, and Frank Perrella

Office of New Drugs, CDER

- Ann Farrell and Edvardas Kaminskas

Office of Compliance

- Francis Godwin

Office of Blood Research and Review, CBER

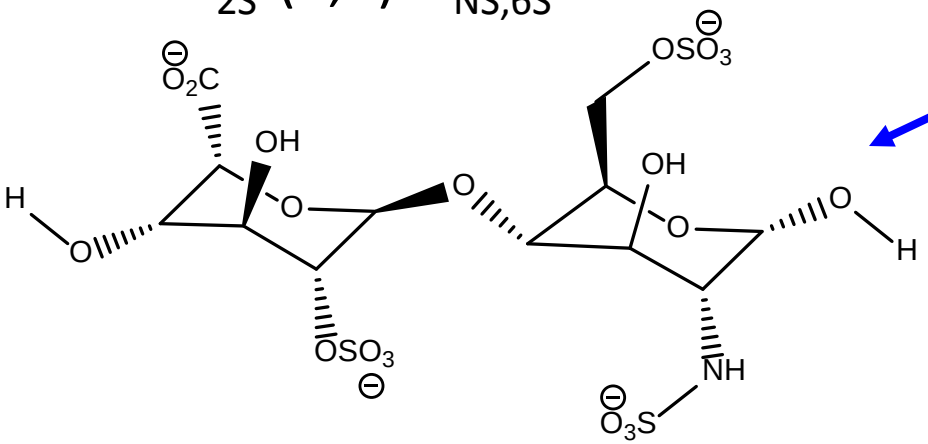
- David Asher and Luisa Gregori

Consults with USDA, CVM, USP and industry stakeholders

FDA Science Board and WG Recommend Supply Diversification

- Heparin sodium is a WHO designated essential, life-saving drug that is needed worldwide.
- ~60% of the supply to the US market comes from a single country and a single species.
- Risk from geo-political instability or disease in a single species source (pigs) could be reduced with diversification of the supply geographically and across species.

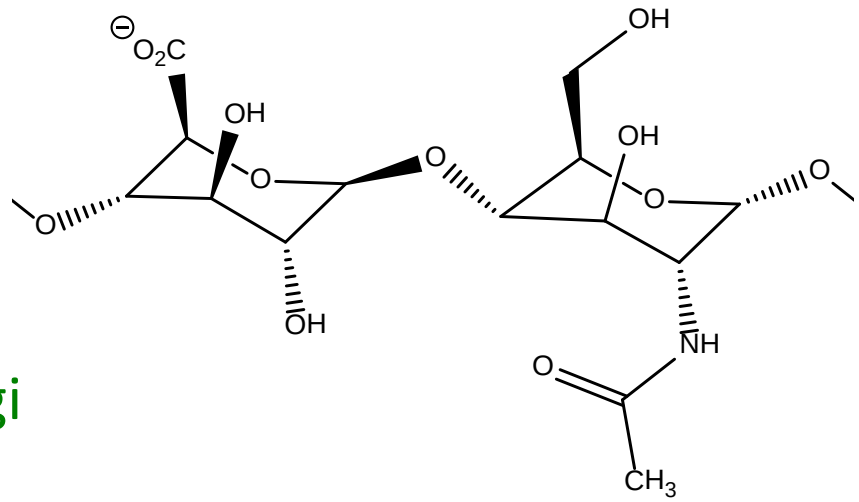
Heparin



~70% of heparin

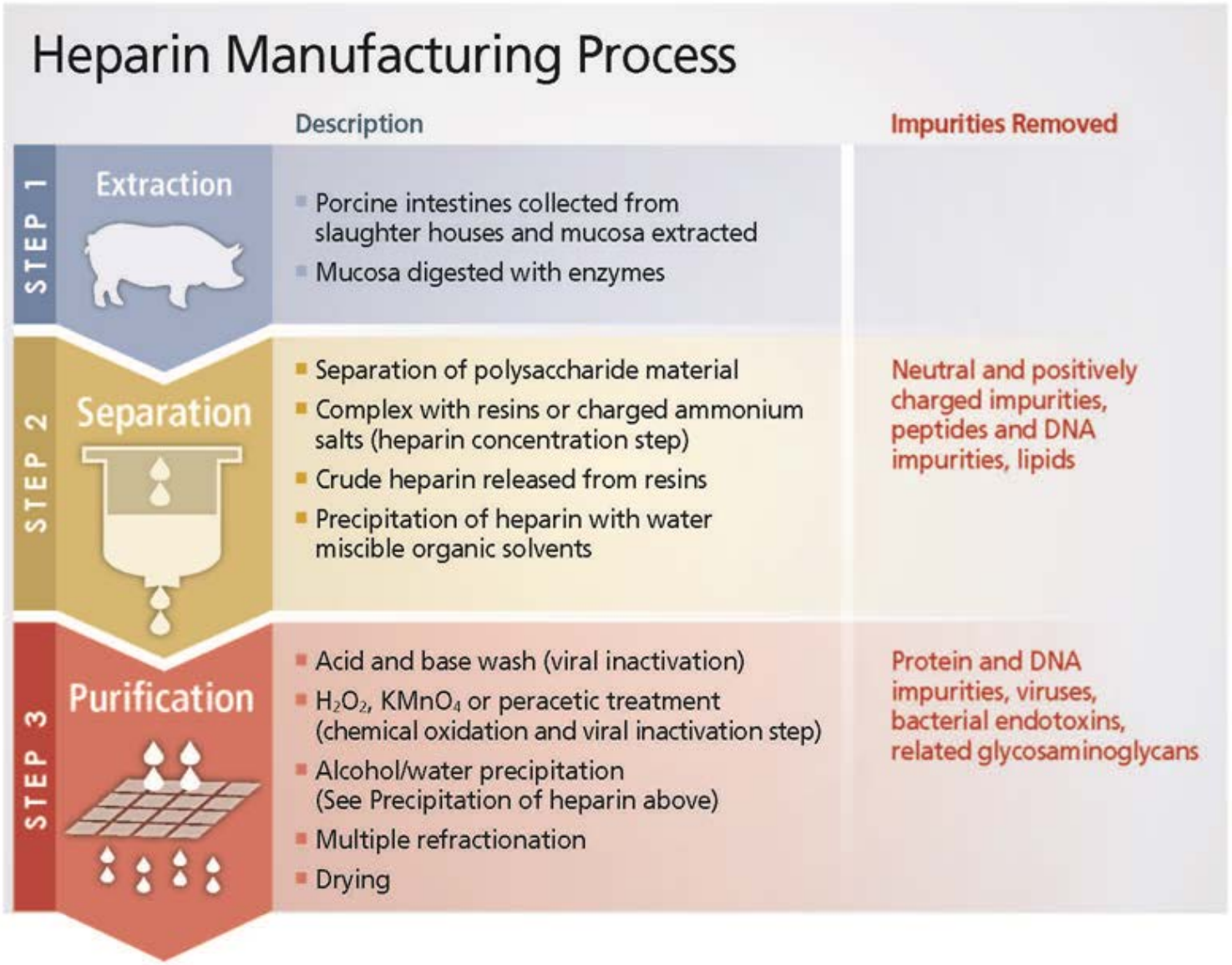
~10% of heparin

~20% of heparin



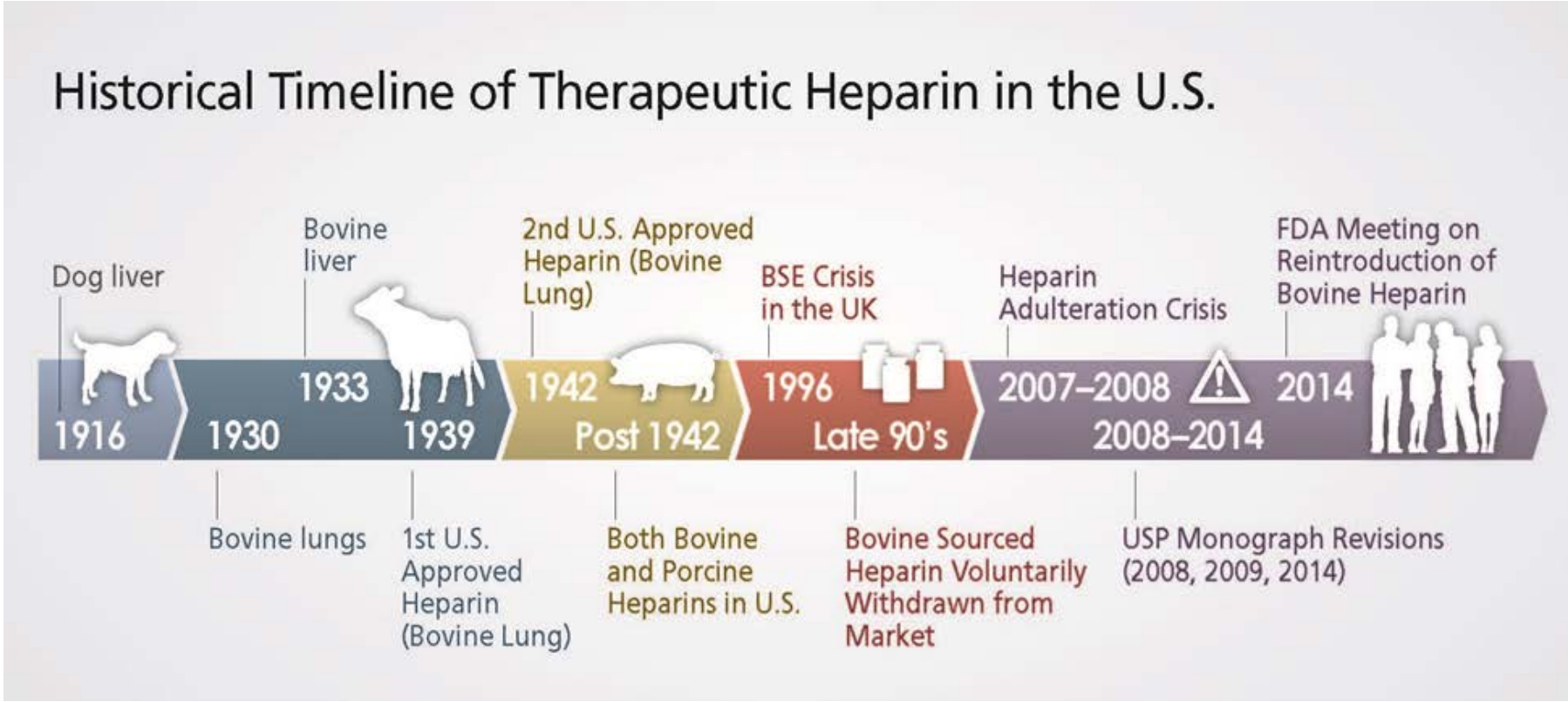
Epimerization and
Sulfation activity in ER and Golgi

Heparin Manufacturing Process



Keire DA, Mulloy B, Chase C, Al-Hakim A, Cairatti D, Gray E, Hogwood E, Morris T, A.S. Mourão P, da Luz Carvalho Soares M, and Szajek A. *"Diversifying the Global Heparin Supply Chain: Reintroduction of Bovine Heparin in the United States?"* Pharmaceutical Technology, 39(11), November (2015).

Heparin History



Keire DA, Mulloy B, Chase C, Al-Hakim A, Cairatti D, Gray E, Hogwood E, Morris T, A.S. Mourão P, da Luz Carvalho Soares M, and Szajek A. *"Diversifying the Global Heparin Supply Chain: Reintroduction of Bovine Heparin in the United States?"* Pharmaceutical Technology, 39(11), November (2015).

Bovine Heparin

- Bovine lung and porcine intestinal mucosa were used interchangeably up to the 1990s.
- Bovine sourced product fell out of favor for two reasons:
  - The pig sourced product was more potent.
  - Concerns with BSE agents and vCJD in humans in the 1990s.

6th USP/NIBSC Heparin Workshop, Sao Paulo Brazil, August 2015

Keire DA, Mulloy B, Chase C, Al-Hakim A, Cairatti D, Gray E, Hogwood E, Morris T, A.S. Mourão P, da Luz Carvalho Soares M, and Szajek A. *"Diversifying the Global Heparin Supply Chain: Reintroduction of Bovine Heparin in the United States?"* Pharmaceutical Technology, 39(11), November (2015).

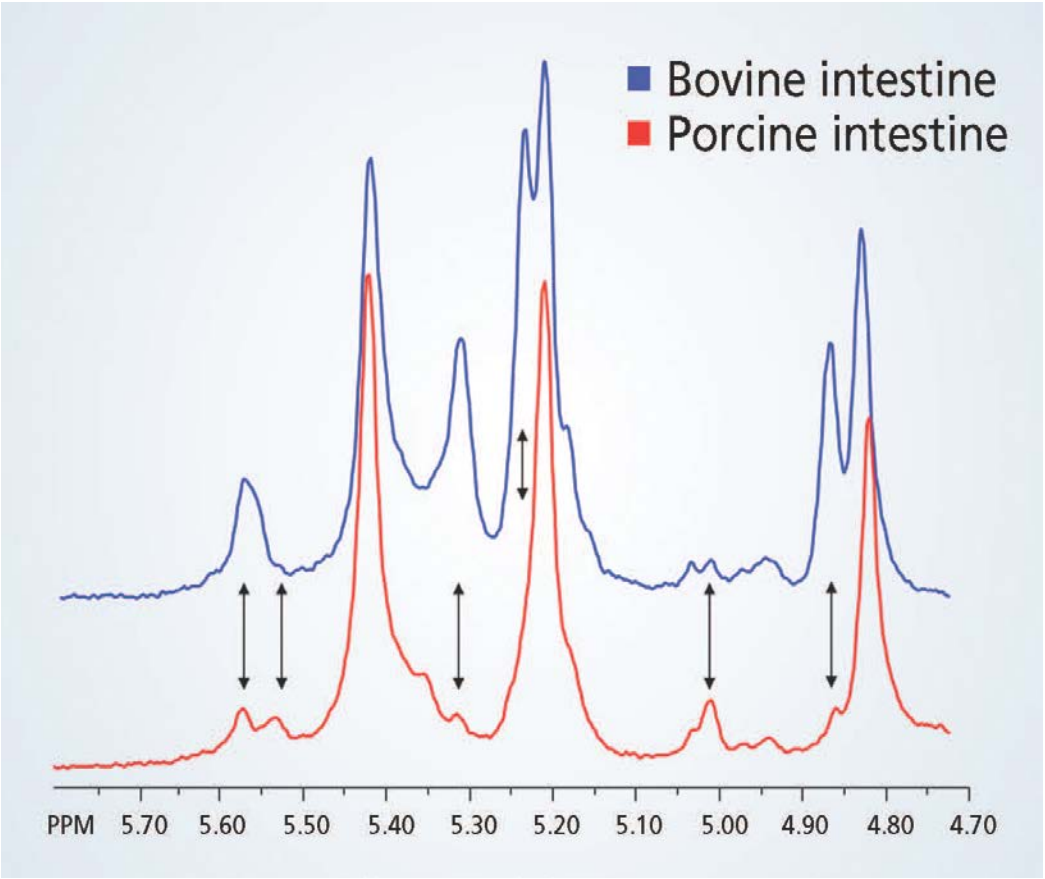
Key Takeaways on Bovine Heparin

- Bovine intestinal heparin is approved for use in Brazil, Argentina and India.
- For Brazil, in 2008, 42% of the market was bovine intestinal heparin.
- By 2013, in Brazil, bovine heparin was gone from the market, in part because of new monograph requirements for NLT 180 IU/mg potency.
- In Argentina, 70% of the market remains bovine and is unchanged in recent years.

Keire et al. Pharmaceutical Technology, 39(11), November (2015).

Similar chemically but with some differences

- New USP monograph will include tests that distinguish heparin types.
- Similar total amount of sulfation.
- Bovine and porcine heparins contain similar monosaccharides with some at different levels.



Keire et al. Pharmaceutical Technology, 39(11), November (2015).

Activity

- The anticoagulation activity of bovine intestinal heparin is approximately ½ of porcine heparin.
  - Heparin is given in units of activity in the clinical setting so twice the amount of bovine intestinal heparin would need to be administered to achieve the same therapeutic effect.
  - Bovine heparin use in the past (US) and currently in other countries suggest that higher amounts given do not impact clinical efficacy.

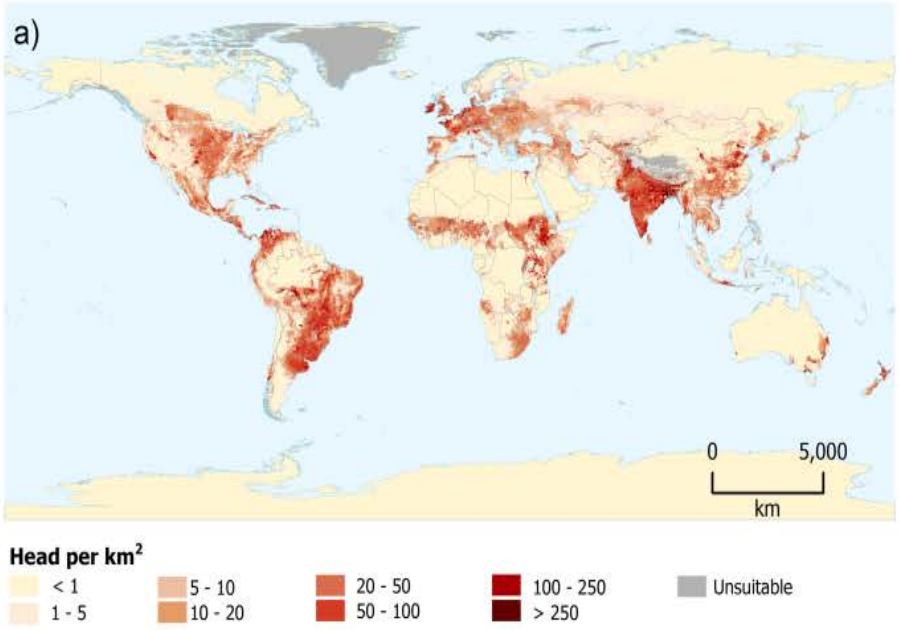
Porcine heparin potency has changed over time

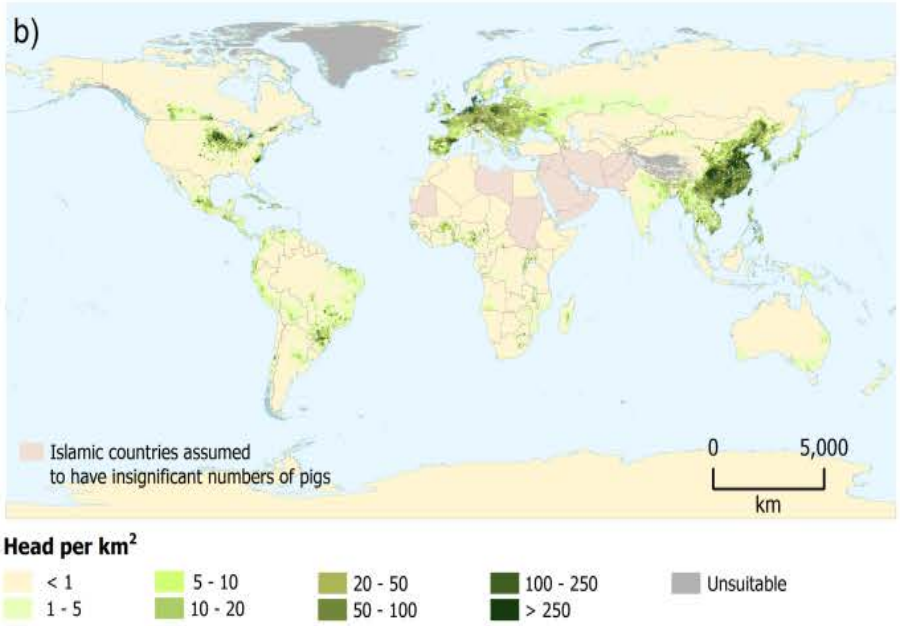
	Neville 1989	FDA 2009	Neville 1989	FDA 2009
Assay	%DS	%DS	Anti-Factor Xa	Anti-Factor Xa
Mean	**5.7 ± 4.4**	**0.3 ± 0.4**	**100 ± 11**	**217 ± 14**
#	19	20	18	20

Doses of porcine heparin similar to bovine heparin dose were given in the past.

Neville GA, Mori F, Holme KR, Perlin AS. *J Pharm Sci.* 1989 Feb;78(2):101-4
Keire DA, Ye H, Trehy ML, Ye W, Kolinski RE, Westenberger BJ, Buhse LF, Nasr M, Al-Hakim A. *Anal Bioanal Chem.* 2011 Jan;399(2):581-91.

Global distributions of cattle and pigs

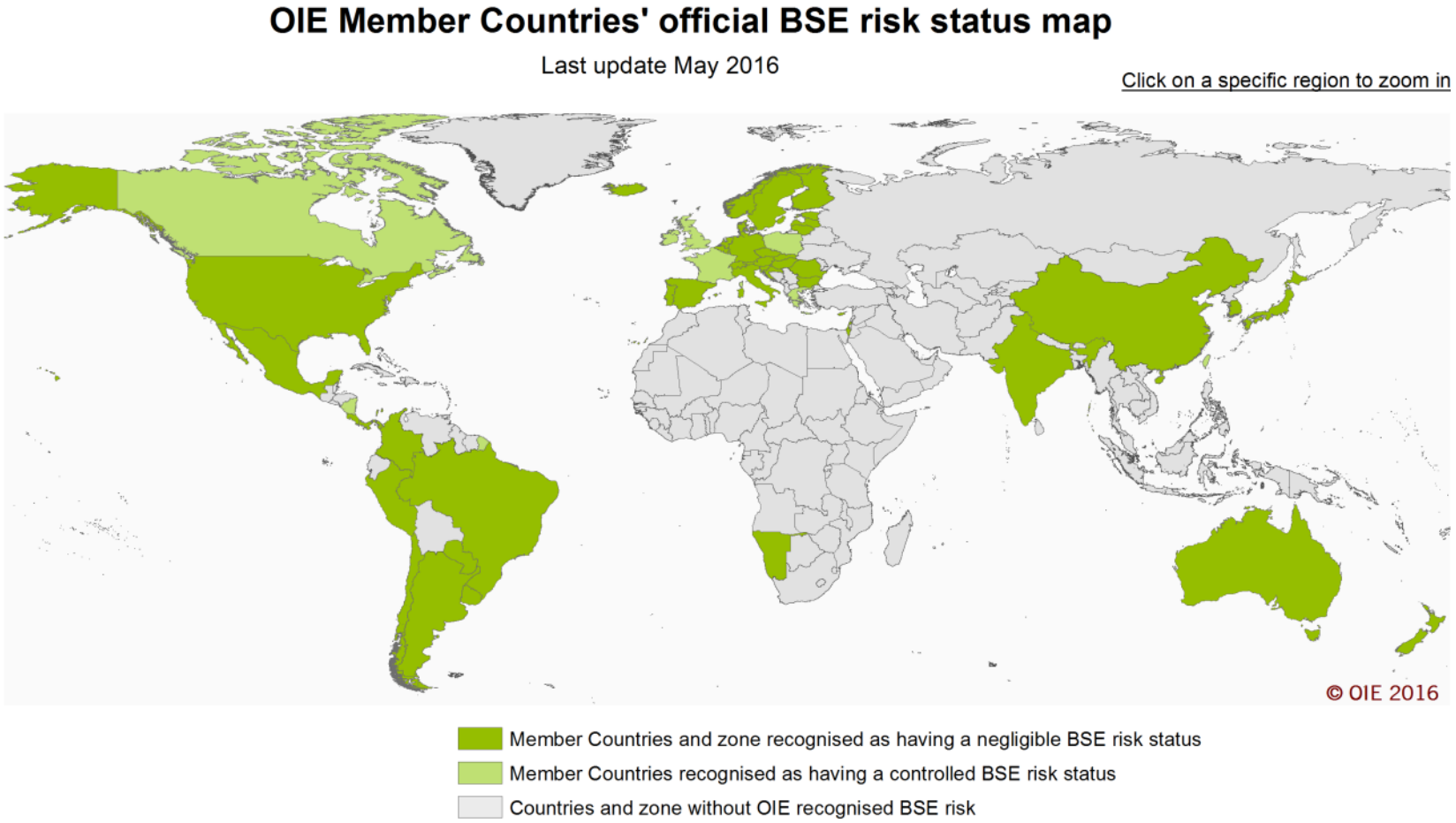




With estimated standing populations of 1.43 billion cattle, 1.87 billion sheep and goats, 0.98 billion pigs and 19.60 billion chickens.

Robinson TP, Wint GRW, Conchedda G, Van Boeckel TP, Ercoli V, et al. (2014) Mapping the Global Distribution of Livestock. PLoS ONE 9(5): e96084. doi:10.1371/journal.pone.0096084
http://journals.plos.org/plosone/article?id=info:doi/10.1371/journal.pone.0096084

Current Global BSE Risk Status



World Organization of Animal Health

Very few recent BSE cases

- "The implementation of appropriate control measures resulted in the decline of BSE worldwide from 37,000 cases in 1992 to fewer than 300 in 2006."
  - http://www.oie.int/fileadmin/Home/eng/Animal_Health_in_the_World/docs/pdf/BSE_EN.pdf
- In 2015 there were reported 7 BSE cases worldwide.
  - http://www.oie.int/?id=505

Future bovine heparin manufacturing

- Drug substance and drug product manufactured under cGMP.
- Supply chain control (*i.e.,* farm, slaughterhouse, facilities used to isolate, store and ship bovine material).
- Prevent cross contamination with high risk tissues at slaughter (CNS tissue).
- Restricted from OIE “Negligible Risk” countries.
- USDA-based ante- and post mortem inspection for animal health.
- Intrinsic capacity of manufacturing procedures to reduce infectivity risk.

Progress

- ✓ 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 complete.
- ✓ Use of RT-QuIC as a proxy for scrapie animal model evaluated.
- Spiked BSE agent removal study (BSL-3 laboratory) initiated with mouse model.
- RT-QuIC for BSE compared to mouse model results.


FDA
U.S. FOOD & DRUG
ADMINISTRATION