FDA Suggests Reintroduction of Bovine-derived Heparin

During an advisory committee meeting with its Science Board in early June, the FDA suggested a reintroduction into the US market of bovine-derived heparin. Despite theoretical risks associated with bovine-derived products, heparin is a vital product for clinical use, FDA representatives argued, and single-animal/country-specific sourcing is risky. Heparin is one of the oldest drugs still in widespread clinical use. It was discovered in 1916, though it did not enter clinical trials until 1935. It was originally derived from canine (dog) liver cells, but now is predominantly sourced in porcine (pig) intestinal cells. Sources for the active pharmaceutical ingredient (API) in heparin are becoming limited, and the FDA sees bovine (cow) sources as the future of keeping the heparin supply robust.

Currently, all heparin products marketed in the US are obtained from the intestinal mucosa of pigs. This includes products approved under new drug applications (NDAs) and abbreviated NDAs, as well as Center for Devices and Radiological Health (CDRH) regulated devices using heparin. China is the source of more than half of crude heparin used in US products; about 75% of all crude porcine heparin used to manufacture the API comes from outside the US. The FDA pointed out that there is little growth potential in both the US and the European Union for porcine sources. Without a reliable foreign supply, the agency chose to look at bovine sources to help diversify the supply chain.

The FDA approved the first application for bovine-derived heparin in 1939, with multiple other applications subsequently approved. In the 1990s, bovine-derived heparin was voluntarily removed from the market by manufacturers due to theoretical concerns related to bovine spongiform encephalopathy (BSE), commonly known as mad cow disease.The BSE agent caused a previously unrecognised variant Creutzfeldt-Jakob disease (vCJD) in humans, most likely due to consumption of contaminated beef products. Notably, to the FDA's knowledge, there has never been a documented transmission of transmissible spongiform encephalopathies (TSEs) to humans from a medical product of bovine origin. This is also true in the United Kingdom, where a very large number of cattle were infected with the BSE agent in the 1980s and 1990s.

The supply of heparin from porcine sources is not without risk, either. In 2008, following reports of serious allergic-type hypersensitivity reactions (including some resulting in death) in patients undergoing dialysis and cases of severe hypotension associated with the use of intravenous bolus doses of heparin sodium for injection, the FDA identified a contaminant, oversulfated chondroitin sulfate (OSCS), in heparin sourced from pigs raised in China. This contamination occurred in the US and in at least 10 other countries. OSCS contamination of heparin appears to be an example of intentional adulteration (or economically motivated adulteration) to reduce the cost of production. In addition to the 2008 incident, questions have been raised more recently concerning the potential risk to recipients of products where heparin may have been used in manufacturing or is present in the final product. These products include plasma-derived clotting factors, including US-licensed antihemophilic factor (Factor VIII), Factor IX complex concentrate, and other plasma-derived products, such as immune globulins and albumin.

Aside from the OSCS contamination, the substitution of bovine heparin to address the risks of porcine heparin poses a special risk of contamination with BSE. The FDA's 2013 G*uidance for Industry: Heparin for Drug and Medical Device Use, Monitoring Crude Heparin for Quality* signals the risk of crude heparin contaminants to manufacturers and recommends new test strategies to be used in addition to the United States Pharmacopeia (USP) monograph testing to detect the presence of OSCS or any non-porcine origin material, especially ruminant material, unless specifically approved or cleared as part of drug or medical device application. In its reasoning for reintroducing bovine-derived heparin to the US market, the FDA stated that much of the clinical data regarding the safety and efficacy of unfractionated heparin was derived from bovine heparin. Though the risk for BSE still theoretically exists, it is better understood and can be effectively managed.

Existing heparin manufacturing processes could have intrinsic capability to remove or inactivate BSE agents, if they are present. In addition, the FDA has guidelines in place regarding TSEs that could be applied to heparin products. The guidelines include information on control of animal sources and the selection of the types of tissue used. Additionally, the FDA suggested development of an alternative assay for detection of BSE infectivity, which could overcome the significant lag time for evidence of BSE disease in traditional animal models.

With proper safety measures in place, the agency argued, heparin sourced from bovine lung cells could be reintroduced to the US market, thus diversifying the supply chain and providing a solution for current shortages.

Molly Fellin Spence is a writer and editor with more than a decade of experience in publishing. She has been employed by Thomson Reuters for three years, specialising in pharmaceutical regulatory affairs as a medical and regulatory writer for the Cortellis database and AdComm Bulletin.
Email: molly.spence@thomsonreuters.com