Making heparin safe

Although manufacturing fraud remains possible, Chinese firms have upgraded their processes to meet stricter U.S. regulations.

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In brief

The 2007–08 heparin scandal caused more than 80 deaths in the U.S. and shook the public’s faith in the safety of drugs, particularly drugs that come from China. Since then, regulators have tightened quality standards for heparin and improved enforcement efforts. Still, questions about heparin’s safety remain. In the pages to follow, C&EN explores the difficulties inherent in manufacturing this unique drug and how one Chinese company is stepping up to the challenge.
The pig is king in China. While North Americans and Europeans prefer to eat beef or chicken, pork is the meat of choice in China. In 2014, China slaughtered more than 700 million pigs, roughly one animal for every two people in the country. Pigs are so much a part of the culture in China that the character for home (家) is made up of two symbols meaning pig and roof.

China’s huge pig population is the reason why the country is a superpower when it comes to making heparin, an anticoagulant used around the globe during heart surgery and dialysis as well as for the treatment of deep vein thrombosis. The country accounts for half of the world’s heparin production.

Pig intestine mucosa is currently the only approved raw material for producing the heparin sold in most of the world, including the U.S. And given that each mucosa yields only a few grams of heparin, China’s huge pig population is essential to the world’s supply of the drug.

Ensuring the safety of a substance that is extracted from pig organs thousands of kilometers away poses a great challenge for U.S. regulators, as well as for companies that source heparin to formulate heparin sodium solutions and other treatments based on heparin.

The risks inherent to this long supply chain became apparent in 2007 and 2008 after hundreds of patients in the U.S. and other countries suffered severe allergic reactions to Chinese heparin that had been adulterated with an unapproved additive. More than 80 people died in the U.S. alone.

Nowadays, the production of heparin is subject to far stricter controls than in 2007, making the repeat of such a tragedy less likely. But risks remain, not only because much heparin is from China but also because heparin is a complex mixture of molecules and therefore cannot be characterized exactly. As the U.S. Food & Drug Administration ponders how to further safeguard the safety of the drug, U.S. legislators continue to raise concerns about the quality of heparin made in China.

It may come as a surprise that a drug extracted from pig intestines persists in the era of modern pharmaceutical chemistry. First introduced in 1935, heparin remains an essential drug with unique properties that synthetic anticoagulants such as warfarin cannot replicate.

It may also come as a surprise that, even after the events of 2007 and 2008, the safety of heparin cannot be assured. Back then, the allergic reactions and deaths were caused by heparin from China that had been adulterated with oversulfated chondroitin sulfate, an animal-derived product that at the time couldn’t be detected. Unscrupulous players added the chondroitin to stretch heparin and lower its cost.

Since then, FDA, the pharmaceutical-standards-setting organization U.S. Pharmacopeial Convention (USP), and their counterparts in other countries have sharply tightened heparin manufacturing standards. Among several new measures, FDA inspectors started making surprise visits to Chinese heparin plants. And USP has outlined new limits for common heparin impurities, including oversulfated chondroitin sulfate, and added new tests to verify the animal species the heparin came from.

This tightening of standards has made it far harder to adulterate heparin, but it hasn’t made it impossible. “I believe that poor-quality Chinese heparin nowadays rarely makes its way to the U.S.,” says Zhengjie Mei, founder and chairman of Hubei Enoray Biopharmaceutical, China’s largest producer of crude heparin. “However, some producers still don’t implement the highest standards.”

Among the several Chinese heparin producers that C&EN approached for this
More than a source of meat
Pig intestines are the source for most heparin, an anticoagulant drug.

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Many competitors buy crude heparin from third parties, Mei says. The company is located by the Yangtze River near the central Chinese city of Jiujiang. The city may not be one of China’s industrial hubs, but within a two-day drive, Enoray has access to slaughterhouses that can easily supply the 15,000 pig intestines the company processes daily.

Enoray staffers are stationed at the slaughterhouses to approve or reject the intestines before they are loaded onto refrigerated trucks that bring the pig parts to Jiujiang. At the Enoray plant, Mei says, employees also visually inspect the organs and reject any bad ones. “Intestines from sick animals are dark, not bright pink,” he notes.

In the initial stage of processing, operators place the intestines into equipment that separates the mucosa, the inner lining of the intestine, from other intestine components such as the casing material sold to sausage makers. The room where this takes place has the pungent smell of fresh meat.

The mucosa is then piped into large vessels for an enzymatic reaction that separates proteins and impurities from the glycosaminoglycans from which heparin is later extracted. Subsequent operations yield crude heparin powder, which is either sold to other companies or processed into pharmaceutical-grade heparin by Enoray itself.

Each operation conducted by Enoray, all the way back to the slaughterhouse, is documented and individually signed by the operators involved, according to Peter J. Werth, chief executive officer of the U.S. pharmaceutical chemical importer ChemWerth. ChemWerth represents Enoray products in the U.S. and advises the firm on U.S. regula-
After the mucosa is collected, crude heparin is extracted by a process involving enzymatic decomposition (shown here), elution, alcohol precipitation, heating, drying, and grinding.

After the 2007–08 scandal, heparin producers were required to add several quality-control steps. A polymerase chain reaction test (shown here) verifies that heparin is from porcine sources.

Crude heparin is further processed into different drug active ingredients such as heparin sodium and tinzaparin. Shown here is an Enoray active pharmaceutical ingredients plant.

Finished heparin is sold in vials by companies such as Sagent Pharmaceuticals and Fresenius Kabi.

China, Miao adds, has more than enough pigs to supply its own heparin needs as well as the export market. Owing to productivity improvements, it now takes about 1,500 intestines to produce 1 kg of heparin, not 2,000 intestines as U.S. lawmakers have claimed. And unlike in 2008, most major slaughterhouses are now overseen by the government, he says, meaning that far more than half of slaughtered pigs are available to heparin producers. “The small slaughterhouses, by definition, they don’t slaughter a lot of pigs,” he notes.

Even if only 300 million pigs are available for heparin in China every year, that’s enough to produce 17.6 million megas of heparin, Miao says, referring to a measurement unit used for heparin. “World demand is 28 million megas, and the rest of the world outside China produces 14 million units. So China has spare production capacity.” Europe is the world’s second-largest heparin producer, accounting for 8 million megas, Miao estimates.

With the beefed-up FDA requirements, it is almost impossible to contaminate heparin with oversulfated chondroitin sulfate, Miao argues. Using other animals remains a vulnerability, he concedes, but all in all, raising compliance requirements much further could raise costs to the point that heparin shortages would start to occur, he says.

Shortages nearly occurred in 2008 when numerous batches of contaminated heparin were recalled in the U.S. and Europe. Looking ahead, FDA has been mulling reintroduction of heparin extracted from cattle “to address such issues as possible shortages..."
and economically motivated adulteration of porcine heparin,” the agency tells C&EN. Bovine heparin was available in the U.S. until the 1990s, when it was discontinued over concerns about bovine spongiform encephalopathy (BSE), or mad cow disease. Bovine heparin is still sold in Brazil, a major cattle producer.

FDA says it is working with USP and foreign regulatory agencies, as well as heparin experts, to develop new standards to characterize and quality test heparin from bovine sources. The agency notes that the risk posed by BSE can be minimized by using cattle raised in countries free of the disease and by using only the animals’ lungs and intestines.

But some scientists contend that reintroducing bovine heparin could compromise heparin safety. “You can expect more unwanted side effects in patients if you use heparin from bovine sources,” says Guangli Yu, a professor in the School of Medicine & Pharmacy at Ocean University of China who studies heparin. Pigs are more genetically similar to humans than cattle are, Yu says, so porcine heparin poses less of a risk of allergic reaction.

“If you want to improve the quality of heparin, turning to another species may not be the right solution,” he says.

Bin Liu, the sales director at Enoray, points out that “bovine heparin may help cut out China as a source of supply, but if you get the threat of BSE in return, you’re not that much ahead.” In addition, he notes that all scientific research on heparin since the 1990s has been based on heparin from porcine sources. It will take a lot of work, and new clinical trials, to determine when and how bovine heparin can perform like the porcine version.

To get around the problem that sourcing heparin from animals poses, one solution could be synthetic heparin or a synthetic drug that performs like heparin. Several groups of researchers around the world are trying to do just that, despite the long odds against succeeding.

“When we first started, we tried to make heparin itself,” recalls Jian Liu, a professor at the Eshelman School of Pharmacy at the University of North Carolina, Chapel Hill, who heads a group that has been trying to synthesize heparin for more than a decade. “But how can you reproduce a molecule that cannot be precisely characterized and that also contains 40 sugars?”

In recent years, Liu’s group has had some success trying to reproduce fragments of heparin containing about a dozen sugars. The group focuses on fragments that have medical activity and that would, in the end, resemble drugs such as Sanofi’s Lovenox that are based on low-molecular-weight heparin. Liu is confident that his group will have a clinical drug candidate within a couple of years.

“We are able to control the size of the molecule so that it can be metabolized in the kidney or the liver, depending on the patient’s condition,” Liu says. His group has also come up with an agent that can reverse the effect of the drug for patients who respond negatively.

While researchers such as Liu continue to explore synthetic versions of heparin, Werth, the API importer, is gearing up to introduce Enoray’s pig-derived heparin to the U.S. Because his firm advises Enoray on regulatory compliance and audits its quality-control systems, Werth is confident that quality will not be an issue.

But he cannot vouch for other companies, even with the higher standards that FDA has imposed in recent years. The problem, he says, is human nature. If there is a way to make more money by adulterating a product, some will be tempted. “You can only take it so far,” he says. “Somebody who wants to cheat will find a way.”

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