



UPDATE ON INVESTIGATION

March 5, 2008

Baxter's first priority is ensuring that its products are safe. In keeping with this priority, Baxter is in pursuit of the root cause of the increase in the allergic-type reactions associated with its heparin sodium vial product to understand the underlying reason(s) for the increase in adverse events that it has seen with its heparin product, and is committed to making sure this critical product is available for all of the patients that need it across the United States. Its scientists and expert consultants have employed a battery of sophisticated analyses to methodically isolate and rule in or out the multiple variables in the manufacturing process and supply chain.

The following is a preliminary update on the status of the company's investigation into the root cause of the increased allergic reactions associated with its heparin product, as well as background information on the product, its manufacture and supply chain.

Update on Investigation and Findings

At this point, Baxter has ruled out the manufacturing process at its Cherry Hill, New Jersey manufacturing facility as a potential contributor to the root cause. The investigation into the elements of Baxter's manufacturing process included an analysis of the components that make up the heparin solution and its packaging (the vial, rubber closure, water, sodium chloride and benzyl alcohol), an extensive evaluation of the data collected during manufacture of the products, and a review of the aseptic processing conditions at the time the products were manufactured.

These investigation results were shared with an investigator from the FDA's New Jersey District Office during the FDA's recent inspection of the Cherry Hill site. **That FDA inspection, which started on January 17, 2008, was concluded on February 28, 2008 with no inspectional observations (known as Form 483 observations) issued.**

Baxter also tested finished product solutions from "test" and "control" lots. "Control" lots are those where finished product was not associated with adverse reaction reports, while "test" lots were those associated with the cluster of adverse reactions. Samples from both control and test lots were analyzed, using appropriate analytical methodologies, for the presence of potential leachables (container components that have the propensity to migrate into drug solutions and subsequently be introduced into the patient) and trace elements (a chemical element present in minute quantities). The leachables and trace element profiles for the control and test lots were compared, and no meaningful differences were observed.

Baxter has used sophisticated nuclear magnetic resonance (NMR) spectroscopy tests and capillary electrophoresis (CE) tests to identify any differences that might have existed in the chemical composition of the control and test lots. The NMR and CE test results for the test lots showed the presence of extra signals and a peak (respectively, for the NMR and CE tests) that were not present in control lots of the Active Pharmaceutical Ingredient (API), which Baxter purchases from Scientific Protein Laboratories LLC (SPL). Baxter is currently focusing on determining precisely what substance(s) the extra signals/peak represent and what its source might be.

The company now has an indication that the observed differences may be due to the presence of a heparin-like molecule. Baxter is not certain that the differences observed in the API are the source of the allergic reactions. Since the extra signals and a peak are the only significant differences noted between control and test lots of API, **the API is now the focus of Baxter's investigation.**

Baxter has since tested samples of API that were processed at SPL's Wisconsin plant, using Chinese-made crude heparin. Baxter's NMR and CE tests found that four out of five of the Wisconsin processed lots that were most recently tested showed the same extra signals/peak that were seen in earlier tests of lots from SPL's China plant. These results suggest that **the root cause may be associated with the crude heparin, sourced from China, or from the subsequent processing of that product before it reaches Baxter.**

Background on Heparin

Heparin is an anticoagulant that has been used for over 70 years and is one of the most commonly used therapies in the United States. It is administered to millions of patients each year in a wide variety of clinical and surgical settings, and is sold in vial form, pre-filled syringe form, and pre-mixed intravenous bag form. Baxter alone sells approximately 50 million vials of heparin every year. As a commodity pharmaceutical, heparin is relatively inexpensive – most vials sell for less than one dollar.

The potential side effects of heparin have been well known for decades, and are well documented in the literature and product labeling. These side effects include allergic-type reactions.

Heparin, while classified for regulatory purposes as a drug, is in reality a complex biologic, derived from the tissues of living organisms, in this case the intestinal mucosa of pigs. Biologics are by nature more difficult to control and produce in uniform fashion, and demonstrate much more variation in composition than a chemical-based drug.

Baxter produces heparin in "single-dose" vials, which can be used only once, in "multi-dose" vials, which can be used either to draw individual doses for multiple patients or used to create a larger bolus dose for a single patient, and HEP-LOCK "heparin flush," which is used to flush intravenous lines and is much more dilute than therapeutic heparin. Nearly all reported adverse reactions that Baxter has received associated with its recent recall have occurred with our multi-dose vials. Baxter has received some reports of allergic-type reactions with higher dose single-dose vials when single doses were combined to create a larger "bolus" dose. Baxter's single-dose vials, multi-dose vials and HEP-LOCK vials are filled using the same API.

Baxter is one of two of the largest suppliers of heparin products to the U.S. market. **Most of the world's heparin API supply comes from China. Production of API within the United States is insufficient to support the large U.S. market need for heparin products.**

SPL's 30-Year History of Supplying Heparin API

Baxter's supplier of API is Scientific Protein Laboratories, L.L.C. ("SPL") located in Waunakee, Wisconsin. SPL originally supplied API to ESI Lederle, a division of Wyeth that Baxter acquired on December 12, 2002. SPL was first listed as an approved supplier of heparin for ESI in 1972. The only product or service that SPL has ever supplied to Baxter has been heparin sodium API. SPL initially provided heparin API that was refined from crude heparin made from U.S. porcine intestinal tissue and finished in SPL's facility in Wisconsin. In the 1990s, SPL began to explore sourcing the crude heparin from China. **From 1996 to present, SPL has produced regular**

shipments of finished heparin API processed at its Wisconsin facility and sourced from Chinese crude heparin material.

In 1999, SPL created a joint venture with Techpool Bio-Pharma Co., Ltd. called Changzhou-SPL (“SPL-CZ”) and later opened a facility for processing crude heparin. This facility was inspected by Wyeth’s Global Compliance Division for a qualification audit to ensure the facility met all cGMP (current Good Manufacturing Practice) requirements and the requirements of the business. The SPL-CZ plant successfully completed the qualification audit in 2003.

In February 2004, Baxter submitted a NDA Prior Approval Supplement (“PAS”) for use of the SPL-CZ facility as an alternate supplier for heparin API. Baxter’s NDA PAS referenced the Drug Master File (“DMF”) that SPL had submitted to the FDA for the SPL-CZ facility. The DMF contains proprietary information accessible to the FDA, but not Baxter, regarding SPL’s manufacturing process. The FDA approved the PAS in June 2004. The SPL-CZ facility began to process crude heparin for Baxter in November 2004 and has been continuously supplying finished heparin API product with Chinese-sourced crude heparin since that time.

Baxter pays the same price for the API, regardless of which SPL facility Baxter gets the material from, Wisconsin or Changzhou, and the price has remained the same since Baxter acquired the product through the ESI Lederle acquisition in 2002.

Baxter’s relationship with SPL is governed by a written supply agreement that requires all API produced to conform to all applicable regulatory approvals, cGMP requirements and all applicable rules and regulations, including the FDA Guide to the Inspection of Bulk Pharmaceutical Chemicals. Other than this contractual supply arrangement, Baxter has no other financial or ownership interest in SPL.

Audits of the SPL-CZ Facility

As noted above, the first audit of the SPL-CZ facility was the full qualification audit performed by Wyeth Global Compliance in December 2002. In September 2003, Baxter conducted a plant inspection, and in November 2004, following FDA approval of the NDA Prior Approval Supplement, Baxter first began receiving lots of heparin API finished in SPL-CZ.

Baxter performed an audit of the SPL-CZ facility on September 20, 2007. This cGMP audit was conducted to verify the effectiveness of the plant’s quality systems and technical capabilities. Based on Baxter’s review of the SPL-CZ facility, Baxter approved SPL-CZ’s continued production of Heparin Sodium USP API pending satisfactory responses to the observations included in the report. SPL-CZ produced satisfactory responses on January 19, 2008.

Based on the successful completion of the audits of the SPL-CZ facility and SPL’s Wisconsin facility, Baxter can summarize SPL’s performance history with Chinese crude heparin prior to current cluster of adverse reactions as follows:

- Twelve years of successful API manufacturing
- Over 500,000,000 finished doses
- Four FDA inspections/audits
- Five Wyeth/Baxter inspections/audits

Baxter’s audit follows the principles of the U.S. Department of Health and Human Services/FDA/CDER/CBER Q7A Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients (“Q7A”), an ICH internationally recognized standard.

The Q7A audit process does not apply to the manufacture of raw materials and intermediates further upstream in the supply chain. Baxter relies upon SPL to effectively monitor and audit its suppliers, which is consistent with general industry practice worldwide, both for heparin and other drugs. Baxter (and Wyeth before it) had a positive track record with SPL – including a dozen years of supplying heparin API made with Chinese-source crude heparin and in excess of 500 million of doses of finished product made from that API.

A critical part of Baxter's processes for ensuring that products meet applicable quality standards is the multiple, rigorous testing done on all lots of incoming API and finished products. As a matter of course, Baxter performs more than 15 separate tests on the API and finished product as required by applicable compendia, in this case, United States Pharmacopoeia (USP) standards. USP is the official public standards-setting authority for all prescription and over-the-counter medicines, dietary supplements, and other healthcare products manufactured and sold in the United States. Even though SPL meets USP standards and provides its raw materials to Baxter with the USP designation, Baxter re-tests every lot of the API to ensure that the incoming material meets both USP testing criteria and Baxter's established standards.

When the company's investigation of root cause is complete, Baxter will examine whether the findings suggest that additional requirements ought to be imposed on SPL or other API manufacturers.

Timeline and Update on Recall

At the end of December 2007, as part of Baxter's normal pharmacovigilance process, Baxter noticed an increase in the rate of allergic-type reactions associated with its 1,000 unit/mL 10 mL and 30 mL multi-dose heparin products. The initial reports came from a few dialysis centers. In response to these initial reports, Baxter's quality specialists analyzed the manufacturing and quality control records for the heparin lots associated with the adverse events. **Quality records showed these lots had met all applicable specifications.** Baxter also reviewed manufacturing change controls from January – December 2007, and found no changes to product, process or specifications that could have contributed to these events. Further, all raw materials (actives and excipients) used to manufacture these lots conformed to specifications.

Baxter initiated a manufacturing investigation to determine the most probable cause, and on January 9, 2008, Baxter placed inventory for both the 1,000 unit/mL 10 mL and 30 mL product on hold. On January 8, 2008, Baxter's pharmacovigilance group also began visiting sites where adverse events were reported. On January 11, 2008, Baxter contacted the FDA about these increased adverse drug experience reports at some dialysis centers. The reports all concerned patients that experienced one or more of the following events after administration of a loading dose of heparin for hemodialysis: hypotension, flushing, lips tingling, abdominal pain, chest burning, feeling warm, feeling strange, fainting, diaphoresis, shortness of breath, thirst and nausea. Baxter also told the FDA that an investigation had been initiated to determine the most probable cause.

After January 11th, Baxter received additional complaints against additional lots of Baxter 1,000 unit/mL 10 mL and 30 mL multi-dose heparin. On January 14, 2008 Baxter suspended the manufacturing of its 1,000 unit/mL multi-dose products pending the outcome of an internal investigation. Baxter communicated this additional information to the FDA on January 16, 2008, and also informed the FDA that Baxter was initiating a voluntary recall. On January 17, 2008, Baxter issued a voluntary recall of nine lots of Baxter's 1,000 units multi-dose product.

After this recall was announced, Baxter saw a slight increase in reactions on other lots and sizes of heparin sodium injection beyond the 1,000 units multi-dose vials that had been recalled.

On February 6, 2008 Baxter contacted the FDA to report that the company was contemplating an expanded recall on the multi-dose vials. On February 8, 2008, Baxter reported to the FDA that there had been 348 unique adverse reaction case reports, with 94% of the reports related to 1,000 unit multi-dose vials, 4% of the reports related to the 5,000 unit and 10,000 unit multi-dose vials, and 2% of the reports related to the 5,000 unit single dose vial (8 total). Three of these eight single dose reports concerned situations where multiple single dose vials were used to create a large bolus dose.

Baxter confirmed with the FDA its intent to recall all multi-dose vials in the marketplace on February 8, 2008. However, since Baxter supplies approximately half of the multi-dose vials of heparin used in the United States, the FDA and Baxter were concerned about the supply of heparin in the market if the recall was expanded. After careful consideration, on February 8th, FDA and Baxter concluded that it was better for public health to allow the Baxter multi-dose vials of heparin to remain in distribution so they could be used with caution in situations where the use of heparin was considered medically necessary and alternate sources of heparin were not available. This decision was announced to health care professionals on February 11, 2008 in a broadly disseminated Important Safety Information Bulletin.

On February 19, 2008, there were press reports about APP, the other major supplier of heparin in the U.S. The press reports indicated that APP had increased production of heparin and that APP had the ability to adequately supply the U.S. market with heparin. Baxter immediately assembled information on its own supply situation, including supply that might become available from non-SPL sources. Baxter initiated a conference call with the FDA on February 22nd and discussed whether it could expand its voluntary recall in light of APP's announcement about their ability to supply the market. The FDA (including the Office of Drug Shortage) wanted some time to examine the issue including market supply of all heparin products. On February 27, 2008, Baxter received final clearance from the FDA that it could recall all of its heparin products from the market. Baxter expanded its recall of this product on February 28, 2008 to include all its multi-dose, single dose and HEP-LOCK¹ products.

Investigation of Adverse Event Reports Associated with Heparin

Baxter monitors drug safety surveillance through its pharmacovigilance (i.e., safety surveillance) group. The pharmacovigilance group receives, investigates, analyzes and reports on adverse events. All adverse events must be reported to the FDA either on an expedited or periodic basis, regardless of whether there was any causal relationship between the use of the product and the reported event.² **Accordingly, due care must be taken in characterizing the number and types of adverse reactions reported to the FDA and the causal association of those reactions to the drug at issue.**

Since December 15, 2007, Baxter has received approximately 450 reports of adverse events. Of those, we believe that at this time, only four patients suffered an allergic-type reaction to heparin that may have contributed to a fatal adverse outcome. Each of these patients had multiple underlying complex medical conditions and three had either undergone, or was in the process of undergoing, invasive cardiac surgery. These complications make it impossible,

¹ Baxter has not received any reports of adverse events for HEP-LOCK in the current adverse reaction cluster. However, because it is manufactured using the same API as the vial-based therapeutic heparin, Baxter included it in its recall expansion.

² Regulatory requirements and pharmacovigilance practice use the term "related" to classify cases where there is a likely causal relationship between an adverse event and a drug, but also in those cases where a lack of information does not allow for the exclusion of a causal link. In other words, a case may be designed as "related" for the purposes of regulatory reporting although there is no data available to actually substantiate a causal relationship between drug and adverse event.

without further medical data, to draw a firm conclusion as to whether these deaths were caused by the allergic reactions. FDA has likewise confirmed that they are aware of four fatalities that have the same clinical characteristics as have been seen with the allergic reactions reporting during this cluster. In addition to these four reports, we have received eight reports where the timing of the heparin administration and the specific medical condition of each patient make it unlikely that these deaths were causally related to the allergic reactions addressed in Baxter's recall. In two further cases, that are the subject of the only litigation so far, no medical professional or family member has provided any medical records or credible information that would allow verification. During the same time frame, Baxter estimates that more than 10,000,000 doses of our heparin product were administered.

The FDA stated last week that they had received 21 reports of deaths from all causes. FDA cautioned very strongly that many of these reports did not contain sufficient information necessary to determine a causal association between the death and heparin from Baxter. This emphatic caution is worthy of careful consideration. As the FDA stated last week, "Just because there's a report in a patient that took heparin doesn't necessarily mean that heparin caused the event. And there are all kinds of events that occur. A lot of these patients are very, very sick." The use, in some press reports, of words such as "linked" or "tied" has created a false impression of a causal relationship when, in fact, the medical facts do not support such a conclusion. For example, the use of the words "linked" or "tied" with respect to the four initial fatality reports that were discussed last month was inappropriate. Our investigation thus far shows that it is unlikely that there is a causal relationship between the allergic reactions and any of these four initially reported patient fatalities.³

The difficulty of characterizing a causal relationship is exacerbated in the types of patients who require heparin therapy: patients with end-stage renal disease, clotting tendencies, acute heart attacks, blood clots in the legs or lungs, or patients requiring cardiovascular procedures, including open-heart surgeries. In such an ill and complex population of patients, deaths are unfortunately more likely to occur for reasons having nothing to do with heparin therapy. It would be medically incorrect to assume that, simply because heparin was present at or around the time of death, it played a causal role in the death. Similarly, to indiscriminately ascribe a "link" or "tie" to heparin in these circumstances is inappropriate from a public health perspective, given the critical role heparin therapy plays in saving tens of thousands of patient lives each day.

The second issue impacting Baxter's pharmacovigilance effort is the wide publicity associated with this heparin recall, which has triggered a substantial increase in adverse event reports, many of which lack the substantial medical detail required to determine whether a heparin product was actually involved in the report, if that heparin product was a Baxter product, and what causal relationship between the reported adverse events and heparin, if any, exists. Typically, these reports are being provided by a patient or a relative of a patient who has no medical training and no access to information about the drug the patient actually received, the

³ In one case, investigation revealed that the patient had not received Baxter heparin. Another case, although reported to Baxter recently, actually occurred in early 2005, almost three years before the increase in adverse reactions that triggered the recall. Additionally, in that case it remains unclear whether the heparin product involved was actually a Baxter heparin product. A third case involved a death as a consequence of bowel obstruction and overwhelming infection, with no evidence of causal association with heparin use. The fourth case involved the death of a cardiac patient in which the role of heparin, if any, was as one of several potential causes of thrombosis, a well-documented side-effect of heparin, and one that is not consistent with the types of adverse reactions reported during the cluster that led to the recall.

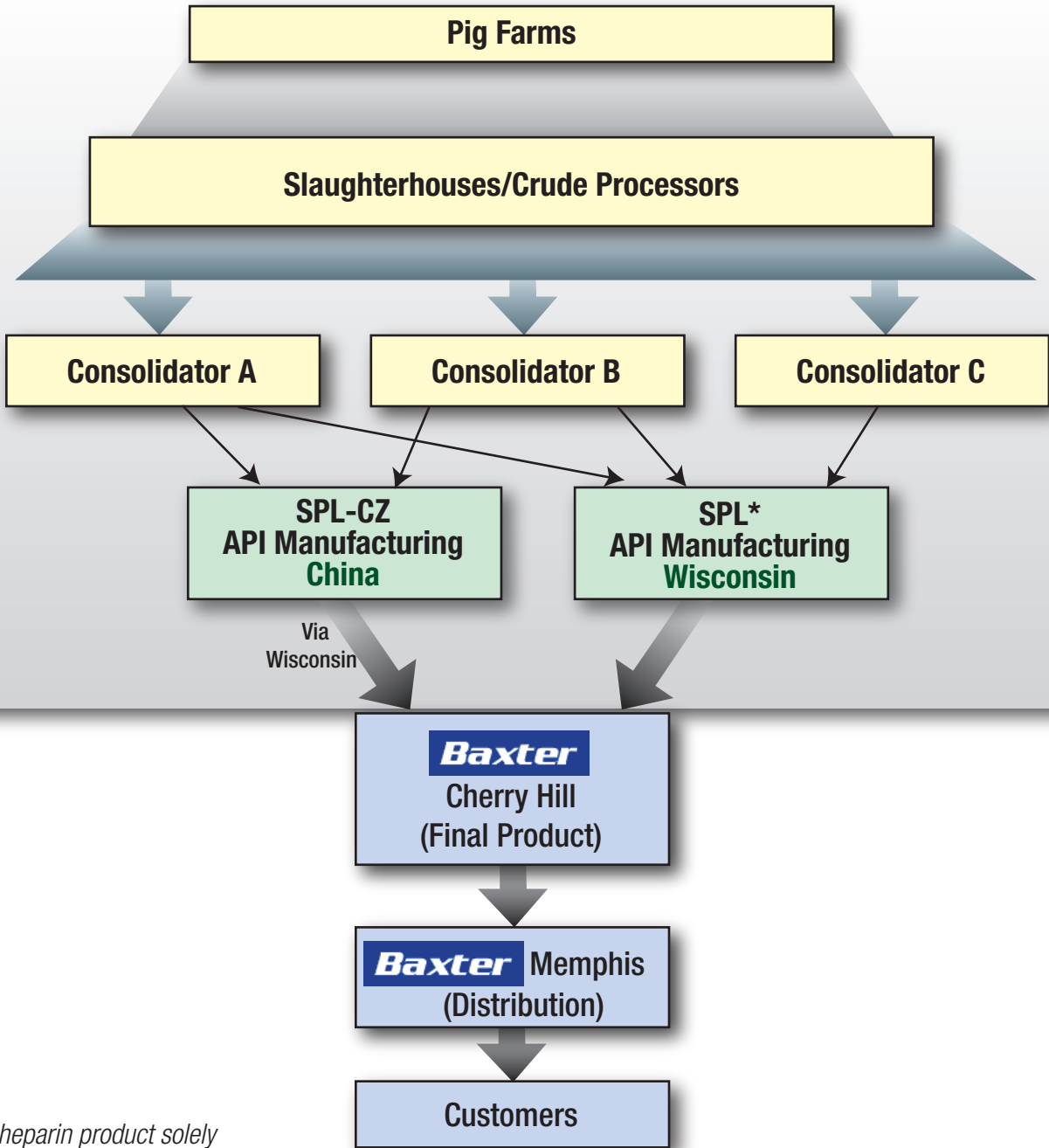
manufacturer of that drug, route of administration or formulation. Baxter's efforts to investigate further have been hampered by the unwillingness of clinicians and hospitals to discuss reports, often at the behest of hospital risk managers concerned with malpractice liability after the mischaracterization of the four initial patient deaths as "linked" to the recall.

Moving Forward

Baxter will continue to investigate and analyze these reports to assess whether the reported adverse reactions were causally related to the cluster of allergic reactions that are the subject of the recall, and will continue to forward all reports received to FDA. The root cause investigation is continuing, and our scientists are working collaboratively with FDA and SPL to pinpoint the source or cause of the heparin-like molecule detected in testing to date.

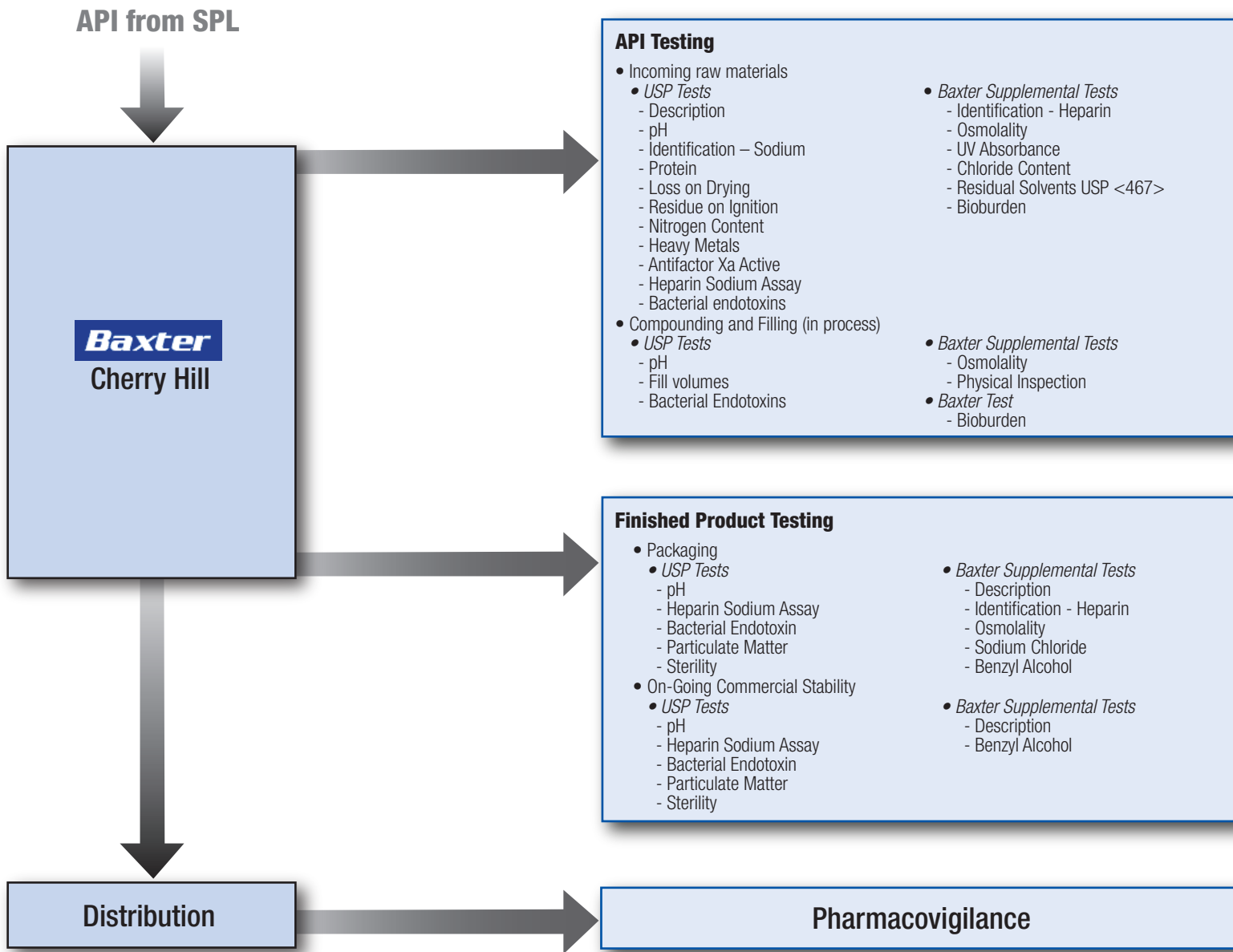
Baxter and FDA have established rigorous quality standards that have been effective for ensuring the safety of heparin for decades and hundreds of millions of doses. In this particular case, those long-standing standards were unable to detect whatever it is that is causing these differences in API. Certainly once more is known about the cause, we will work closely with regulatory authorities and others responsible for developing industry standards to ensure that necessary changes in standards and processes are made.

Baxter Heparin Supply Chain

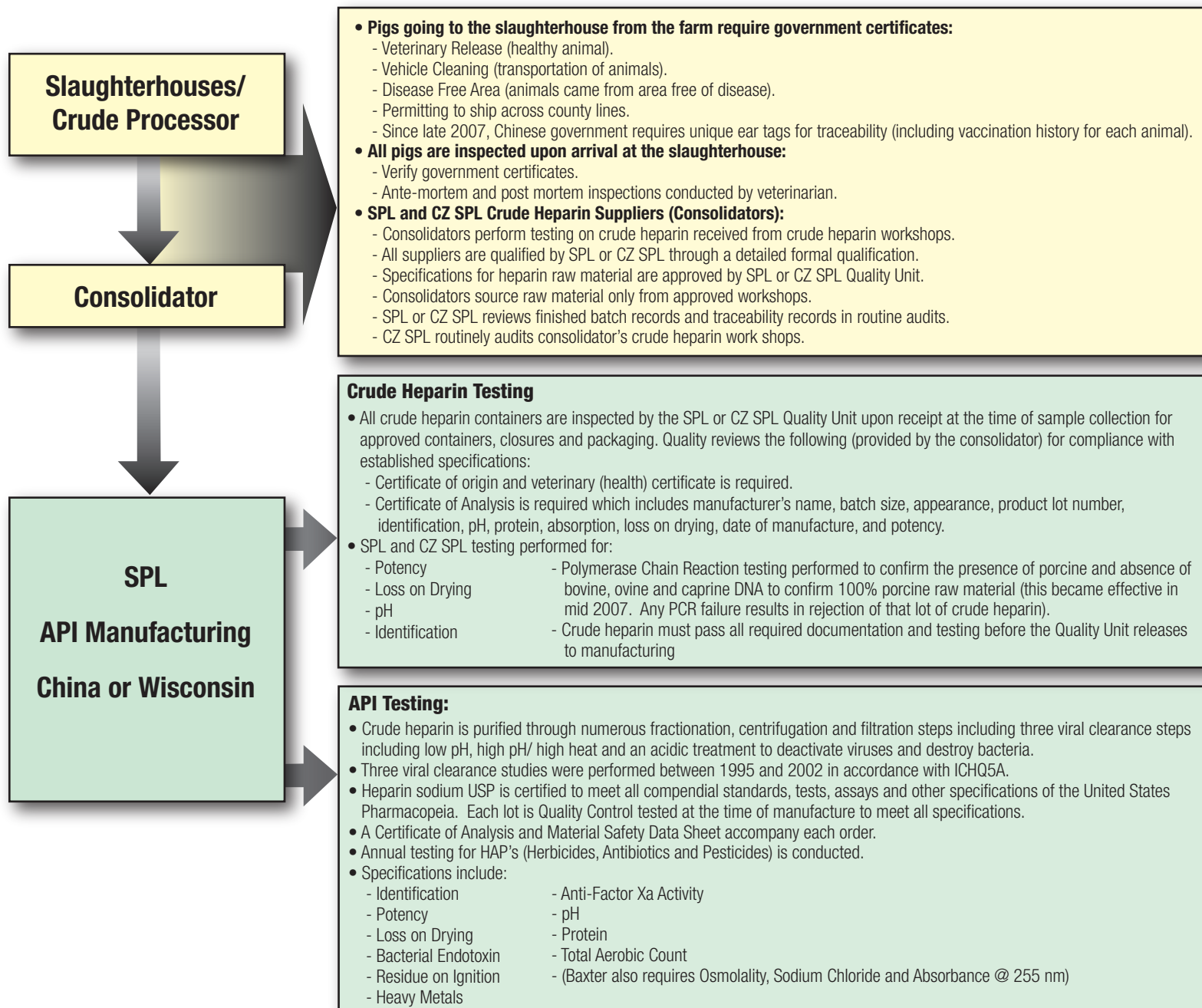


**This facility also manufactures heparin product solely from pig farms and slaughterhouses in the U.S.*

Baxter Quality Tests

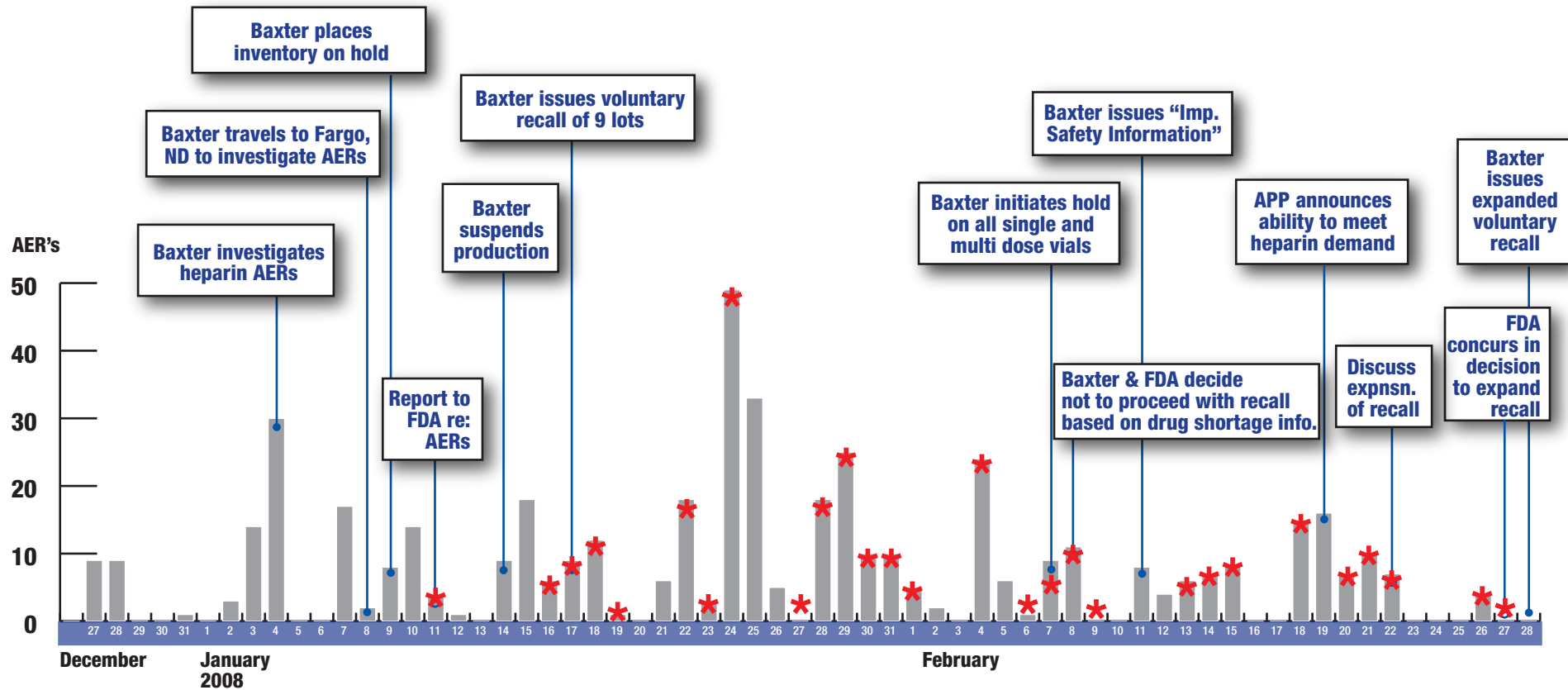


SPL Quality Tests*



*Based on information provided by SPL regarding its current processes and testing.

Summary Of Baxter's Response To Adverse Events



* Baxter's Contacts with FDA regarding AERs.