INTRODUCTION

To ensure the purity and safety of unfractionated heparin (UFH), effective October 1, 2009, the U.S. Pharmacopeia (USP) implemented several modifications to the current standard in its monograph for UFH. The changes update methods of identifying UFH contents and characterizing the potency and purity of the active pharmaceutical ingredient (API) and the resultant finished product.

A further change addresses an estimated drift of 10% between the USP unit and the International Unit (IU) for UFH over the past 30 years. The drift has resulted in an average of 10% (range, 7%-13%) higher potency in products prepared according to the USP standard, compared with those prepared with former USP potency standards. The change aligns the USP reference standard with the international standard and creates a 10% increase in apparent potency for the API, which then leads to 10% less heparin in the final drug product. These changes in standards apply to all manufacturers of heparin marketed in the U.S.

To the obvious question of whether a specific conversion factor needs to be used for dose modifications, there is no clear-cut answer. Although the decrease in potency of the UHF finished product prepared with the new USP standard has averaged within a 7% to 13% range, various authorities (the FDA, the USP, and APP Pharmaceuticals) have stopped short of such a recommendation, citing the inherent low and variable bioavailability of heparin, lot-to-lot manufacturing variations, and the general sense that the change will not have clinical significance beyond current limits requiring monitoring of activated partial thromboplastin time (aPTT) or activated clotting time (ACT). The potential for heparin contamination, according to the FDA public health alert concerning the monograph change, is lessened because the production of a high-quality drug has been enhanced and new testing methods can detect impurities that the older method could not.

The FDA alert suggests that when heparin is given subcutaneously, concern for clinical consequences is minimal because of the already mentioned low and variable heparin bioavailability. However, in other circumstances, such as with an intravenous (IV) heparin bolus given when an immediate anticoagulant effect is clinically important, health care professionals may need to consider the change when choosing a dose. Heightened attention to monitoring is recommended for prescribers, and the FDA has advised patients that they might be subjected to increased monitoring.

Crystal Rice, Trade Public Affairs Specialist from the agency’s Center for Drug Evaluation and Research (CDER), said that the FDA was working with manufacturers to obtain in vitro human blood anticoagulation data regarding dose-response relationships for incremental dose alterations (e.g., 10%) and is also working to obtain similar data from in vivo animal studies.

WHAT HAPPENED?

In an interview, USP Vice President of Biologics & Biotechnology Tina Morris, PhD, noted that during the heparin contamination crisis, which developed in late 2007 and early 2008, the FDA quickly identified the contaminant in heparin as oversulfated chondroitin sulfate. The agency approached USP, asking USP to validate its identification methods—capillary electrophoresis and proton nuclear magnetic resonance (NMR). Validation requires that these methods be accurate, reproducible, and robust.

USP’s validation of these two tools led to the incorporation of capillary electrophoresis and proton NMR into the heparin sodium monograph, published as a Revision Bulletin, and met the immediate need to prevent contaminated heparin from entering the U.S. market. The issuing of these bulletins, Dr. Morris explained, is the most rapid USP revision mechanism, and on June 18, 2008, the revised heparin sodium and heparin calcium monographs were published as part of the stage 1 revisions.

On April 22, 2008, shortly before these revisions were published, The New York Times reported that the FDA had made the link between contaminated heparin and 81 deaths in 11 countries. Research published in New England Journal of Medicine (June 5, 2008) took up the challenge of determining whether oversulfated chondroitin sulfate, found to be contaminating worldwide heparin supplies, was responsible for severe anaphylactoid reactions reported after IV heparin administration in the U.S. and Germany. The authors found that oversulfated chondroitin sulfate could directly activate the contact system and could induce the generation of C3a and C5a anaphylatoxins in vitro. It could also activate kallikrein in vitro and induce a profound hypotensive response in pigs, offering a potential biologic link between the contaminant and the reported anaphylactoid reactions.

OVERSULFATED CHONDROITIN SULFATE

Heparin is made from porcine intestinal mucosa. The heparin-manufacturing process is quite complex, Dr. Morris said, and results in a number of naturally occurring and process impurities, among which is chondroitin sulfate. Oversulfated chondroitin sulfate, the contaminant found in products coming from China, is not among the naturally occurring impurities, she emphasized. It is derived by the chemical modification of chondroitin sulfate to the oversulfated form. Chondroitin sulfate has, at most, very little heparin-like activity; however, if it is oversulfated, it actually mimics heparin activity. It costs a fraction of the ingredient usually used in heparin.

Dr. Morris commented: “The impulse behind this substitute process was pure profit. Chondroitin sulfate, which is typi-
cally used as a dietary supplement, is very inexpensive compared with heparin. There’s a tremendous economic incentive driving the adulteration.”

Why didn’t the earlier testing methods detect the presence of oversulfated chondroitin sulfate? Laura Provan, USP Director of Media Relations, noted:

The original purpose of monographs was to identify what something is rather than to make sure that it wasn’t something else. In the pre-global sourcing world, the pre-international adulteration world, there wasn’t any need to devise tests to identify specific contaminants or adulterants. Now we have to start getting more proactive and more defensive, fighting the criminal mind. It’s an unfortunate new world, but that’s where we are.

ARE WE SAFE?

The growing number and worsening nature of threats to pharmaceutical products are of concern to the USP but are beyond the thrust of the USP monographs. Dr. Morris explained:

“Can your monograph catch all potential contaminants? In light of what happened with heparin, we’ve done our best to put methods in place that would catch most naturally occurring impurities and process impurities—and oversulfated chondroitin sulfate. But that isn’t the purpose of the monograph, and we don’t know which drug may be targeted next for adulteration. It is very difficult to anticipate how somebody would try to manipulate a drug, especially a complex and heterogeneous biological product.

With the publication of the stage 1 revisions, the USP heparin panel began work immediately on stage 2 revisions. Dr. Morris explained:

“We had needed to do something very, very fast. But we also realized that the heparin sodium monograph definitely needed some modernization.”

Between June and December 2008, the panel members worked with heparin manufacturers, academicians, regulatory agencies, and other stakeholders to improve the overall quality of the heparin sodium and heparin sodium injection monographs. The resultant revised monograph, published in March 2009, became official on October 1 of this year.4

UPGRADING THE MONOGRAPH

For the identification component of the monograph, the two orthogonal methods were introduced so that if the proton NMR test missed something, the next test would succeed. The capillary electrophoresis test was replaced with a more sensitive one, anion-exchange high-performance liquid chromatography (AEX-HPLC). In the potency-testing phase, the old sheep plasma-clotting assay was replaced by a new chromogenic assay. The sheep plasma-clotting assay, Dr. Morris explained, is a nonquantitative test that is deceived by oversulfated chondroitin’s mimicking of heparin activity.

The detection of organic impurities was enhanced by limiting total galatosamine in hexosamine to 1%—and through three other tests for nucleotidic impurities—for the manufacturing process’s residual solvents (e.g., ethanol) and for host protein (Lowry’s test). The Lowry procedure is one of the most venerable and widely used protein assays, first described in 1951.5

“Since you are extracting heparin from the porcine intestinal mucosa, there are many naturally occurring impurities that the manufacturer has to remove,” Dr. Morris said.

APP Pharmaceuticals, Inc. the largest supplier of heparin sodium to the U.S. market, has launched an educational Webinar series with industry experts about the USP monograph stage 2. In the first installment, Edith A. Nutescu, PharmD, Clinical Professor of Pharmacy Practice at the University Of Illinois College of Pharmacy, stated that implementation of the stage 2 USP standards for UFH provides an opportunity to review relevant protocols and determine the need for modifications.

“Combined with patient variability, timing, and desired response, the potency variation may require more frequent or intensive aPTT or ACT monitoring,” said Dr. Nutescu.

The potential variation for 50 USP units, she suggested, might be within 45 to 55 units; similarly for 500 or 5,000 UPS units, the potential variation might be between 450 and 550 and 4,500 and 5,500 UPS units.

She added: “Practitioners should consider the potential clinical and laboratory impact of such variation.”

Among potentially affected conditions and situations, she cited venous thromboembolism, acute coronary syndrome, surgery, stroke, atrial fibrillation, central venous catheters, intensive-care units, heparin flushes and protamine sulfate reversal. Dr. Nutescu also listed dosing protocols, nursing protocols and orders, pharmacy protocols, standard orders, aPTT and ACT monitoring schedules and targets, dosing nomograms, dilution protocols, pump instructions, and inventory needs. Future webinars are planned to address the implications of the heparin changes in specific clinical conditions.

THREE YEARS OF LOT VARIATIONS

Perhaps the trickiest aspect of the changeover for hospitals will be that they will simultaneously have heparin lots in stock manufactured according to differing standards. That situation, Dr. Nutescu commented, will persist over the three-year shelf life of heparin. An overlap of product, the FDA alert said, is necessary to guarantee that an adequate supply of heparin is available for all patients. The FDA has asked heparin manufacturers to ensure that labeling will help health care professionals differentiate new products from the old by placing an “N” in the lot number or following the expiration date. The FDA also recommended that products manufactured by Hospira be identified by the number “82” or higher (e.g., 83, 84) at the start of its lot numbers.

Indicative of the fact that all changes pursuant to the new heparin standard are potential is that the FDA-labeling for heparin, including the recommended doses, has not changed. The FDA alert states:

“Individualization of heparin dosing has long been the standard for clinical use of the drug and FDA reiterates the importance of clinical judgment in heparin dosing.”

Finally, although the FDA states that it is working with heparin manufacturers to study the impact of the variation in potency, FDA representatives at this time had no information about such ongoing cooperative monitoring with hospitals or other institutions.

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REFERENCES


