U.S. Pharmacopeia
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Heparin Statement
April 11, 2008

There is heightened public interest and concern about the safety of imported medicines, particularly following the recall of certain heparin products in January of 2008 after numerous patients suffered severe allergic reactions.

On March 19, the Food and Drug Administration (FDA) contacted the United States Pharmacopeial (USP) Convention to ask for assistance in resolving an apparent case of adulteration involving heparin-containing drug products available in the United States. While many such drug products are available, two appeared to be particularly at risk. These are therapeutic heparin multi-dose vials, and the heparin lock flush solution manufactured by Baxter Health Corporation and APP. USP welcomes the opportunity to work with FDA and others to address this important public health issue.

USP's role in this possible case of adulteration relates to monographs in USP's primary publication, the *United States Pharmacopeia* (*USP*). Under federal law, heparin and other drugs sold in the U.S. must meet the monograph requirements in the *USP*. This law was created more than 100 years ago, and tied FDA and USP in a unique public-private partnership to help assure the quality of medicines.

FDA first approved heparin drug products for sale within the U.S. in the 1940s, and the *USP* has had a heparin monograph since 1950. Currently, monographs for two heparin drug substances and several drug products can be found in the *USP*. These have been updated on several occasions.

If preliminary reports are confirmed, the adulteration of heparin drug products occurred by addition of over-sulfated chondroitin. Because it can mimic the anticoagulant properties of heparin, the oversulfated chondroitin could appear to be heparin in some of the tests described in the *USP* monograph. Thus the basis for adulteration would be commercial: substitution of a lower cost material (the over-sulfated chondroitin sulfate) for a higher cost material (heparin drug substance). It is unclear at this time whether the observed adverse events are due to the oversulfated chondroitin, to an impurity in this material, or to other factors.

USP's laboratories are now assessing screening methods that could be used to detect the presence of oversulfated chondroitin sulfate in the heparin drug substance before it is made into heparin drug products. If this effort is successful, USP will add methods to the Identification test in *USP* heparin drug substance monographs to test for oversulfated chondroitin. Under U.S. law, if a heparin drug substance tested positively for oversulfated chondroitin, it could not be called heparin and could not be used by a drug product manufacturer in heparin-containing drug products.

USP notes the following:

- It is difficult for any set of analytical procedures in a *USP* monograph, or in a manufacturer's private tests approved by FDA, to detect adulterants such as over-sulfated chondroitin. This is because analytical procedures tend to find known, not unknown impurities.
- Chondroitin sulfate is used orally in the U.S. as a dietary supplement. Manufacture of chondroitin sulfate for this purpose may occur in the same facilities that supply crude heparin. Chondroitin sulfate, oversulfated or not, is not intended for intravenous administration, as are many heparin drug products.
- USP is working closely with FDA and other partners to understand the heparin problem and to come to good solutions. Some of these solutions might be implemented in the near future, and some may take more time.
- The availability of a good public monograph in the *USP* with allied reference materials is one of a series of safety nets that work to assure that U.S. patients and practitioners have access to good quality medicines. Other safety nets include dedicated and trusted drug ingredient and product manufacturers who follow good manufacturing practices

Headquarters
12601 Twinbrook Parkway
Rockville, Maryland 20852
+1-301-881-0666

Europe/Middle East/Africa
Münchensteinerstrasse 41
CH-4052 Basel, Switzerland
+41 (0)61 316 30 10

USP–India Private Limited
ICICI Knowledge Park
Genome Valley
Labs 7-10, Phase III
Turkapally, Shameerpet
Ranga Reddy District
Hyderabad 500 078, A.P., India
+91-40-2348-0088

USP–China
Building 11
Lane 67 Libing Road
Zhangjiang Hi-Tech Park
Shanghai, 201203, China
+86-21-51370600

USP–Brazil
WTorre Technology Park
Avenida Ceci, 1600
Barveri
São Paulo, Brasil

www.usp.org

(GMPs) and sound sampling protocols in support of batch release testing. Oversight from FDA is also key in assuring product quality and safety along complicated and at times lengthy supply and distribution pathways.

USP will provide further information as its work evolves. For updates on the availability of this information, please contact Laura Provan at lnp@usp.org or 301-816-8268.