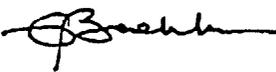


MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: July 10, 2001

FROM: Gary J. Buehler 
Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration

SUBJECT: Cefuroxime Axetil Monograph – Crystalline Forms

TO: The Executive Committee of the Council of Experts
United States Pharmacopeia

As you know, the United States Pharmacopoeia (USP) recently requested that the FDA participate in the upcoming hearing regarding GlaxoSmithKline's (GSK) appeal to the revision of the Cefuroxime Axetil Monograph. The Agency does not object to the proposed change in the monograph and believes that it should be made effective on August 1, 2001. The following discussion outlines the Agency's rationale for this position.

Cefuroxime axetil is a broad-spectrum cephalosporin antibiotic. The drug substance as currently used by GSK is amorphous and contains a fixed ratio of diastereoisomers called isomers A and B. The current USP monograph, the labeling for Cefin[®], the former antibiotic monograph for cefuroxime axetil, and the approval of Cefin[®] were all based on cefuroxime axetil products containing the amorphous form exclusively, which GSK states is critical to achieving optimized bioavailability and dissolution.

GSK requests that the proposed change in the monograph be rejected until the USP adopts appropriate controls on the ratio of crystalline to amorphous forms and appropriate controls on the ratios and identity of the polymorphic forms. GSK states that this is to assure that each batch of the drug product and each lot of the drug product when tested on stability can reasonably be expected to perform comparably to the batch or batches that were tested *in vivo* in support of requested regulatory approval.

GSK indicates that differences in the solid state form of cefuroxime axetil, including the crystalline form, can be significant with respect to safety and effectiveness but cannot reliably be controlled by standard product performance testing. They state that the different solid state forms vary widely in solubility with demonstrable consequences for absorption and bioavailability. GSK also proposes that rigorous and extensive controls for drug substance and drug product, based on the potential issues associated with polymorphic forms in general and cefuroxime axetil in particular, are a necessity for a safe and effective product.

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The Agency's position regarding the issues raised by GSK follows:

In the process of approving abbreviated new drug applications (ANDAs), the Agency must assure that satisfactory standards of product quality are met. Part of this assurance consists of drug substance and drug product controls and specifications capable of maintaining these standards for product quality. Control for solid state forms is one of the criteria that the Agency evaluates. Controls for material quality, manufacturing, and product characteristics are used to provide assurance that the expectation of safety and effectiveness is met.

The USP is an official compendium (21 U.S.C. §321(j)) and the Agency does utilize USP monograph statements and requirements in the evaluation of ANDAs. However, we recognize that there are times when an otherwise suitable official article may differ from the identity prescribed in the USP because the identity statement was based upon a single approved product. It is not always possible to anticipate which characteristics in physical form all articles may achieve.

FDA's determination that a generic product has the "same active ingredient" refers to the same salt or ester of the same active moiety. Differences in physical form, including various solvation states or specific polymorphs, are not part of the understanding of "sameness" under the Federal Food, Drug, and Cosmetic Act (Act). Such differences may, however, be important characteristics requiring controls so as to assure reproducible quality and performance of the drug product. In such cases, additional standards may be imposed beyond those of USP.

The present USP monograph and the related discontinued CFR monograph address physical form as appropriate to the product and manufacturing materials which were in existence then and were proposed at that time. There are established procedures for changing the USP as there were procedures for changing the CFR monographs in response to the development of additional materials and products.

GSK also mentions ICH guidelines. The intent of ICH guidelines on the solid state form of the drug substance is not to preclude or eliminate change, but rather to highlight areas of change where development of additional data may be necessary to justify certain differences. Morphic form may be a critical parameter, and extensive evaluation must be performed when changes are contemplated for a defined product.

GSK has indicated that there are a number of possible solid state forms for cefuroxime axetil. Therefore, rigorous control must be used for these materials. Regardless of the particular solid state form used in a product, the Agency's normal review process includes evaluation of control of the material used for product manufacture. When there is concern that changes may occur in the product that may affect product performance, assurance is required that such changes are capable of being monitored and that product specifications are such to preclude changes detrimental to the product performance.

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GSK provides a description of the ICH recommendations and has shown that there may be significant physical differences between the various solid state forms of cefuroxime axetil. The Agency requires adequate controls to be in place to assure that critical product characteristics are maintained. In addition, the Agency requires that bioequivalence to the reference listed drug must be demonstrated in each application prior to approval. With such assurance, applications may be approved. The specifications that the Agency approves for the drug substance may not be changed until after the Agency has reviewed and approved a supplement to the approved application requesting a change.

Evaluation of the adequacy of controls is part of the normal review process when considering an ANDA. Determinations of the need for such controls are made based on the specific product. Regardless of the controls GSK uses for its product, appropriate controls for the ANDA product are required as a condition of approval. These controls may be different and/or in addition to the controls for the NDA product.

The discussion regarding the content of a specific Ranbaxy patent for cefuroxime axetil, although of interest, is not relevant to the Agency's decision. Approval decisions are based on information contained in Drug Master Files and the submitted ANDA. It is this application-based data that is used to evaluate the adequacy of controls to ensure acceptable parameters for the product. We do acknowledge that processing of either a drug substance or drug product might contribute to changes in the materials, but these issues are also taken into consideration during the normal review process.

The Agency also agrees with the statement from Dr. Steven Byrn (see GSK attachments, page 8 of Byrn statement) that "the scientific and regulatory considerations . . . deserve serious attention and are important to the public health." In fact, this is the reason that a complete scientific review of materials, processes, controls, and bioequivalence demonstration is performed before a generic product may be approved and introduced into the marketplace.

In summary, the Agency believes that the proposed changes to the Cefuroxime Axetil Monograph are in line with past USP practices. In addition, the Agency believes that it has adequate procedures and safeguards in place to assure that any product it approves will be therapeutically equivalent to the reference listed drug. These procedures include controls for the drug substance, drug product and demonstration of bioequivalence to the reference listed drug. Therefore, the Agency has no objection to the proposed monograph becoming effective on August 1, 2001. Finally, as stated in our February 8, 2001, letter to the USP, the Agency has no objection to the future revision of this monograph to state that if the product is a mixture of crystalline forms, the bulk drug substance should include the percentages of the various crystalline forms of Cefuroxime Axetil on its label. This revision should have no impact on whether the current monograph is finalized, since the Agency would establish controls for this aspect of the drug substance in the individual application.

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