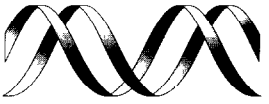

CELLTECH

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June 12, 2003

Dockets Management Branch
Food and Drug Administration (HFA - 305)
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, MD 20852

RE: Comments to Docket #03P-0091/CP1

Dear Sir or Madam:

Celltech Pharmaceuticals, Inc. (Celltech) is the sponsor of the approved new drug application (NDA) for Tussionex® (Hydrocodone Polistirex and Chlorpheniramine Polistirex) Pennkinetic® Extended Release Suspension for the relief of cough and upper respiratory symptoms associated with allergy or a cold. Celltech submits these comments in opposition to the citizen petition noted above of Robert W. Pollock of Lachman Consultant Services, Inc. filed by FDA on March 7, 2003. The petitioner requested that the FDA declare that Hydrocodone Polistirex and Chlorpheniramine Polistirex Extended Release Capsules (the "Proposed Generic Product") are suitable for submission as an ANDA to the reference listed drug product of Tussionex®. The Federal Food, Drug and Cosmetic Act ("FFDCA") directs the FDA to deny a suitability petition if it finds "that investigations must be conducted to show the safety and effectiveness of the drug or of any of its active ingredients, the route of administration, the dosage form, or strength which differ from the listed drug." 21 U.S.C. §355(j)(2)(C)(i).

Celltech respectfully urges the FDA to deny the petition for the following reasons:

1. The reference listed drug uses a unique ion-exchange polymer matrix system with a coated drug resin of hydrocodone and an uncoated drug resin of chlorpheniramine. As this is a complex formulation, the FDA should carefully review and consider the science used in the Proposed Generic Product's formulation, including issues relating to the manufacturing, release specifications and in vitro testing methods, particularly considering the long half-life of chlorpheniramine.

2. The petitioner has requested that this petition be granted based on a claimed increase in convenience to the patient for a capsule dosage form but have provided no evidence to support this assertion. The widespread acceptance and use of the approved Tussionex® Suspension formulation of hydrocodone and chlorpheniramine demonstrates favorable patient reception of a liquid dosage

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form in the treatment of mild to moderate cough. In particular, patient or dispensing confusion may be expected based upon the long history and aesthetics of cough-cold products in liquid formulations.

3. The petitioner has not adequately addressed the potentially reduced convenience, and possible risk of harm, of ingesting a capsule among those patients who have difficulty swallowing a capsule but no difficulty swallowing a suspension. Crushing or otherwise altering the integrity of the capsule or its contents would likely have unintended adverse safety consequences.

4. Celltech believe that these undesirable consequences for patients would offset any potential increase in convenience to the patient claimed by the petitioner by a solid dosage form, even if any minor conveniences can be demonstrated.

5. The approval of a capsule product by reference to a listed suspension product will inevitably result in mislabeling of the proposed capsule product, particularly with respect to dosing and administration. Prescribers have noted, and dispensers confirm, that the potential areas of mislabeling and the potential consequences of mislabeling include, but are not limited to, the following:

   a. The petitioner has requested a half-dose strength capsule. This could create confusion and increase the potential for calculation errors by prescribers and/or pharmacists in having to convert mL of the listed suspension product to an equal number of milligrams per capsule and number of capsules per dose. In addition, having to administer multiple capsules per dose detracts from any perceived convenience of a solid dosage form and increases the potential for therapeutic error, potential overdose and/or misuse.

   b. The proposed half-dosage strength could result in physicians presuming that contraindications and other use restrictions should be taken less seriously for the lower dosage formulation. This could also impact the adverse event profile of the different products, particularly with regard to the vulnerable pediatric population. Further, safety issues associated with the physical properties (e.g, capsule size and texture) of a solid versus a liquid dosage form have not been addressed (e.g., evaluation of esophageal erosive effects should the capsule get lodged in the throat; patient allergy, sensitivity or objection to components of the capsule shell). The physical properties of the capsule formulation would be especially important in patients with gastroesophageal reflux (GERD), particularly with the bedtime dose.

   c. Finally, there could be confusion over whether a capsule could be crushed, sprinkled or split in some manner, and the effects of chewing the capsule contents would need to be explored. The labeling for Tussionex® obviously does not address these issues. The fact that this product is a controlled substance further complicates this issue in that crushing the capsule contents

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circumvents the extended-release availability of hydrocodone and could enhance abuse potential.

6. No data have been presented on the issue of what food effect differences would exist between the capsule dosage form as opposed to the suspension, particularly if the release mechanism of the proposed capsule product differs in such a way as to be vulnerable to effects of pH or drug-food interactions. It would be reasonable to presume that there would be potential food effect disparities between these very distinctive dosage forms, and that such an effect could be clinically meaningful. The FDA's Guidance for Industry on "Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Considerations" (March 2003) acknowledges the possible clinically significant difference of such a food effect. The petitioner provides no information as to how the FDA might conclude whether a significant food effect may be present. If the Proposed Generic Product does show a food effect, then the pharmacokinetic differences may be significant enough to warrant more robust safety or effectiveness studies.

7. There is an unknown increase in abuse liability of an alternative dosage form, especially a solid in this case, that is not accompanied by its own data assessing the abuse liability for that particular dosage form. The sponsor of any such controlled substance should be required to assess the potential for misuse, abuse or overdose of its particular product, which would be outside the scope of the citizen petition.

Conclusion

The petitioner has the burden of establishing in the citizen petition that the Proposed Generic Product can be expected to have the same therapeutic effect as the reference listed drug. 21 CFR §314.93(d)(2). For the reasons set forth above, the petitioner has not met this burden. Under §505(j)(2(C)(i) of the Federal Food, Drug and Cosmetic Act, the petition should be denied upon a determination that investigations must be conducted to show the safety and effectiveness of the dosage form for the Proposed Generic Product, which differs significantly from that of the reference listed drug.

Thus, for the foregoing reasons, we respectfully request that the Commissioner deny approval of the citizen petition.

Sincerely,

Gail Norris
Vice President and General Counsel

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