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OVERNIGHT COURIER 8/1/03

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

Re: Docket No. 03P-0091/CP1
Response to June 12, 2003 comments submitted by Celltech Americas, Inc.

Dear Sir or Madam:

On June 12, 2003, Celltech Americas, Inc. (Celltech) submitted comments to the above-referenced docket in regard to a petition submitted by Lachman Consultant Services, Inc. on March 7, 2003 (filed on March 10, 2003) requesting the Commissioner of the Food and Drug Administration to declare that an ANDA may be submitted for Hydrocodone Polistirex and Chlorpheniramine Polistirex Extended-Release Capsules (equivalent to 10 mg Hydrocodone Bitartrate and equivalent to 8 mg Chlorpheniramine Maleate) and Hydrocodone Polistirex and Chlorpheniramine Polistirex Extended-Release Capsules (equivalent to 5 mg Hydrocodone Bitartrate and equivalent to 4 mg Chlorpheniramine Maleate). This correspondence, submitted in quadruplicate, replies to the Celltech comments.

It is important to note that the comments raised by Celltech are issues that are premature or of such a nature that can and will be addressed in the review of the proposed ANDA. The FDA evaluates many of the issues cited by Celltech in its normal review of the chemistry, manufacturing and controls information, the labeling information and the bioequivalence information required to be submitted in an ANDA by the applicant. If the applicant cannot adequately demonstrate to the Agency's satisfaction that it has met the standard approval requirements, the FDA will simply not approve the ANDA.

The FDA must approve the suitability petition if the requested change from that of the reference-listed drug does not raise questions of safety or effectiveness. The petition proposes a drug product to provide the same dose of the same ingredients for the same conditions of use as provided by the reference listed drug product only in an extended-release capsule rather than in an extended-release suspension. Typically, in a request for a change in dosage form, there are generally no safety or effectiveness questions that could be raised by such a request, especially if the proposed product can be shown to be bioequivalent to the reference listed drug product. Changes in dosage form and strength represent the majority of all ANDA suitability petition types approved by the Agency.

The issues related to market forces or convenience are beyond the purview of the FDA and the market itself will dictate the success of any given product. However, it is difficult to accept the argument that a patient, who does not like the taste of the innovator's suspension or who may

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prefer not to have to shake the suspension well and pre-measure the appropriate volume prior to administration, would not find the proposed product more convenient or acceptable.

Each of Celltech's comments is specifically addressed below. For convenience, each comment is reproduced in full in italics followed by our response.

Celltech Comment 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.*

Petitioner's Response to Comment 1

> The issues identified in Comment 1 are those that relate to the principles embodied in the review of an ANDA. The petitioner would expect that the FDA would evaluate these issues as part of its ANDA review process. This, however, should have no bearing on whether or not to approve the suitability petition.

Celltech Comment 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 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 formulation.*

Petitioner's Response to Comment 2

> As mentioned above, the issue of convenience relates to patient-specific acceptance. Celltech is correct that liquid dosage forms are well-accepted dosage forms for the treatment of cough; however, there are numerous examples of solid oral dosage forms that have liquid counterparts with the same active ingredients. The availability of variations in dosage form can provide both the physician and the patient flexibility in selecting a product to meet the specific needs of the patient and treatment objectives. Celltech is also correct when it indicates that their product has been well accepted, however, there is no bioequivalent alternative dosage form available at this time, and therefore it is possible that the proposed product will also be accepted by those patients who would prefer to take a capsule version of the same medication. Again, however, the fact that the innovator product is well accepted is not a basis for denial of an ANDA suitability petition.
>
> The FDA has approved numerous changes in dosage form through the suitability petition process. This request is no different than many others the Agency has approved. The

petitioner is not aware that such approvals have resulted in "patient or dispensing confusion".

Celltech Comment 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.

Petitioner's Response to Comment 3

The commenter here attempts to use the converse argument to that of the petitioner. That is, there are certain patients who cannot take or have difficulty swallowing capsules. Obviously, this product would not be appropriate for an individual who has such a problem. It would, however, provide the physician an alternative for patients who could not tolerate the suspension or did not want to be bothered with the use of a measuring device necessary for appropriately taking a liquid medication. The decision to prescribe the proposed product would be one made between the health care provider and the patient based on the needs and/or preferences of the patient. The issue of altering the capsule product prior to administration can be dealt with in the product's labeling. This is a common issue among extended-release products, where the patient is instructed to swallow the capsule or tablet whole, without chewing, crushing or emptying the contents of the capsule. In fact, 21 CFR 314.94(6)(B)(ii) clearly contemplates, when necessary, changes in the RLD labeling to contain "information about the different route of administration, dosage form or strength that FDA may require".

Celltech Comment 4

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

Petitioner's Response to Comment 4

Celltech appears to be referring to the issue addressed above regarding certain patients who may have difficulty in swallowing a solid oral dosage form. The intent of the petition is to make an alternative dosage form available for those patients who would prefer a solid oral dosage form (in this case a capsule) over the existing suspension and provide the physician an option in meeting that need. It is the physician's responsibility to assess whether a capsule or liquid would be appropriate or desirable for each individual patient. A physician would certainly not prescribe a capsule for a patient that indicated they had difficulty in swallowing solid oral dosage forms. This is a decision that must be left to the patient and the health care professional; however, the underlying safety or effectiveness of a bioequivalent capsule dosage form should not be called into question. Many prescription drug products are available in both liquid and solid oral dosage form (tablet or capsule) for the purpose of matching the appropriate dosage form to the needs

of the patient. In addition, the Agency has approved many petitions for a change in dosage form from either a solid oral dosage form to a liquid or vice versa, since the availability of different dosage forms obviously meets the needs of various patients.

Celltech Comment 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 a perceived convenience of a solid dosage form and increases the potential for therapeutic error, potential overdose and/or misuse.*

Petitioner's Response to Comment 5a

a. It is unclear to the petitioner how such errors could be made, since the reference listed drug's dosing recommendations are clear. For adults, 5 mL (1 teaspoonful or one dosage unit) may be given every 12 hours with a maximum of 2 teaspoonfuls in a 24-hour period. This clearly translates, in the proposed product, to one capsule every 12 hours with a maximum of 2 capsules in a 24-hour period for adults. For children, the dose as cited in the RLD product's labeling is ½ teaspoonful every 12 hours with no more that one teaspoonful in 24 hours. This clearly translates to one of the proposed half-strength capsules every 12 hours with no more than 2 of the half-strength capsules to be given in 24 hours. There are no instructions in the innovator labeling for multiple doses in a single dosing period for adults or for children and, accordingly, there will be no such instructions in the proposed capsule product. As a matter of fact, having the dose in a capsule and not having to rely on measuring the dose may actually prevent the administration of an inappropriate dose. It is well known that the volume of teaspoons vary significantly[1] (ranging from 2.5 mL to 7.8 mL). Administering the doses as described in the innovator labeling (1 teaspoon (5 mL) every 12 hours for adults) provides potential for a 50% dosing error, which is magnified in the pediatric dosing instructions by introduction of the imprecise concept of "½ teaspoon". The petitioner believes that the suspension product actually has inherently greater potential for significant dosing error than a capsule product such as that proposed here.

Celltech Comment 5b

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 dose 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.

Petitioner's Response to Comment 5b

b. The labeling of the proposed product would have the same warnings, contraindications, precautions and information as that of the reference listed drug product. Why would one presume that a capsule that contained the exact same amount of drug as one-half teaspoonful of the reference listed drug product would cause physicians to take the precautions and contraindications less seriously? This is inconsistent with the fact that many products are available in both a liquid and solid oral dosage form and are also available in multiple strengths with the same warnings, contraindications and precautions. The availability of an alternate dosage form should not, as claimed by Celltech, have an impact on the adverse event profile of the differing products. It should be noted that Tussionex products, prior to their reformulation (i.e. from containing phenyltoloxamine to chlorpheniramine), were marketed in tablet and capsule, as well as suspension, dosage forms. There appears to have been no issue of the safety of the drug product in multiple forms during its prior marketing.

   In addition, the active components of the proposed product are available in various solid oral dosage forms. Chlorpheniramine is also available in extended-release solid oral dosage forms in both capsule and tablet versions. Hydrocodone is available in numerous dosage forms in combination with acetaminophen, aspirin and ibuprofen. The size of the proposed capsule product, based on the dose, will likely be significantly smaller than many of the currently marketed combination hydrocodone-containing products. Due to the historical safety of the two active components already in solid oral dosage forms, additional data should not be required. All inactive ingredients used by the petitioner can be found in the Inactive Ingredient Guide, including those components for the capsule and, therefore, have been used in CDER-approved dosage forms.

Celltech Comment 5c

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

Petitioner's Response to 5c

c. This issue regarding the appropriate method of administration of the capsule can be effectively dealt with through proper labeling of the drug product. The petitioner is

confident that collaboration with the Agency will provide final printed labeling that will adequately address dosing instructions, including recommendations for use of the capsule form. The fact that there are numerous immediate-release drug products with hydrocodone components far in excess of the doses contained in the proposed extended-release capsule product (2.5 mg or 5 mg) lessens the argument that the proposed product would somehow have a greater abuse potential than existing immediate-release or liquid products. In addition, the fact that the hydrocodone component of the proposed product is tightly bound to the polistirex resin should serve to further reduce such concerns.

Celltech Comment 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 differences 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.

Petitioner's Response to Comment 6

The approval of an ANDA suitability petition is a determination that an ANDA may be submitted for the types of change permitted under the statute from a reference listed drug product. Petition approval does not guarantee that an ANDA will ultimately be approved for the proposed change. Acceptability of the ANDA for approval is a matter that is taken up during the review of the application itself. The petitioner agrees that in order for any ANDA to be approved for an extended-release capsule version of the extended-release suspension that the applicant must demonstrate that the proposed product is bioequivalent to an equivalent dose of the reference listed drug product under both fasting and fed conditions (since this is an extended-release formulation). Unless the applicant provides that information in its application, any ANDA for the proposed product cannot be approved. However, this is not a basis for denial of the petition, but rather a review issue that comes into consideration only after the petition is approved and the ANDA is submitted.

Celltech Comment 7

There is an unknown increase in abuse liability of an alternate dosage form, especially in 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.

Petitioner's Response to Comment 7

> As mentioned above, hydrocodone is available in many other approved products in immediate release strengths well above those proposed in the product that is the subject of this petition. To believe that the approval of another solid oral dosage form, in an extended-release formulation at a dose lower than other available immediate-release products and in which the hydrocodone is bound to a resin from which it should not be easily extracted or released, would have abuse potential any greater than the existing products does not seem reasonable.

Again, the petitioner is confident that the issues raised by Celltech are the type that should be addressed in the review of the ANDA. The proposed change in dosage form and strength as requested in the original ANDA suitability petition does not raise any questions of safety or effectiveness and the petition should be approved. It represents a routine change in dosage form that the Agency has approved hundreds of times and it is clear that the proposed change in strength (i.e. the half-strength capsule) is clearly contemplated in the reference listed drug product's labeling.

Sincerely,

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cc: Martin Shimer (Office of Generic Drugs)

[1] Pediatric Counseling and Medication Management Services: Opportunities for Community Pharmacists. Journal of the American Pharmaceutical Association. July/August Vol. 42, No. 4, pp. 558 – 559

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