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Division of Dockets Management
Food and Drug Administration
5630 Fishers Lane, Room 1061
HFA-305
Rockville, MD 20852

RE: Docket No. 2004P-0390
Comments to Suitability Petition

Dear Sir or Madam:

We are writing regarding the above-referenced suitability petition, submitted by Lachman Consultant Services, Inc. (Lachman) on August 31, 2004 (Appendix A). This petition seeks a determination that doxycycline hyclate tablets, 75 mg and 100 mg are suitable for submission in an abbreviated new drug application (ANDA). The reference product cited in the petition is FH Faulding Company's Doryx[®] Capsules (coated doxycycline hyclate pellets, NDA 50-582).

We believe that Lachman has suggested an inappropriate Reference Listed Drug (RLD) in this suitability petition with an inappropriate labeling change, which will result in confusion among medical practitioners and patients using these pharmaceutical agents. A summary of our position is as follows:

- (a) Vibra-Tabs[®] (doxycycline hyclate film coated tablets, Pfizer Labs, NDA 50-533) is a currently marketed tablet approved as a Reference Listed Drug (RLD), and is the most appropriate RLD for Lachman's proposed doxycycline hyclate tablet.
- (b) The clinical pharmacology description of Doryx[®] Capsules is identical to that of Vibra-Tabs[®], so there is no legitimate scientific reason to request a change in product formulation via the RLD.
- (c) The labeling provided by Lachman includes a change in dosing and administration from the labeling of Doryx[®] Capsules, which has not been explained or referenced, which highlights one important distinction between the capsule form and the tablet form of this drug, providing a further reason for not approving the suitability petition submitted by Lachman.

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- (d) If FDA approves the Suitability Petition using Doryx[®] Capsules (coated doxycycline hyclate pellets) as the RLD for another doxycycline hyclate tablet, there will be a great deal of undue confusion on the part of patients who use and practitioners who prescribe these products.

I. BACKGROUND

On August 31, 2004, Lachman Consultant Services, Inc. submitted a suitability petition stating that FH Faulding Company's Doryx[®] Capsules (coated doxycycline hyclate pellets, NDA 50-582) is a suitable RLD for a new doxycycline hyclate tablet, 75 mg and 100 mg. Lachman gave the following explanation as to why the change in the dosage form from capsule to tablet is warranted:

" . . . in this instance, citing any of those products as the RLD would not be appropriate, since the purpose of this petition is to seek the ability to file a different dosage form (tablet) that is bioequivalent to Doryx[®] (doxycycline hyclate) Capsules (coated pellets). The petitioner is seeking this change in dosage form in an effort to make an alternate dosage form (tablet) available for those individuals that either have difficulty in swallowing a capsule or who prefer a tablet dosage form as an alternative to Doryx[®] (doxycycline hyclate) Capsules (coated pellets)."¹

This explanation is unfounded in light of the fact that there is a doxycycline hyclate tablet currently on the market that provides a more appropriate choice of RLD. Vibra-Tabs[®] (Pfizer, NDA 50-533) is an approved oral tablet, appropriate as the RLD. There are also seven other generic oral tablets on the market (Axiom Pharm, Ivax Pharms, Mutual Pharm, Mylan, Vintage Pharms, Watson Labs, and West Ward; see Orange Book listing in Appendix B), all 100 mg tablets.

II. ARGUMENT

A. The RLD Vibra-Tabs[®] (doxycycline hyclate film coated tablets, Pfizer Labs, NDA 50-533) is the most appropriate RLD for the generic doxycycline hyclate tablet under development.

Vibra-Tabs[®] (Pfizer Labs) is an oral tablet that could be used as an appropriate RLD for the 100 mg dosage form of doxycycline hyclate tablets proposed by Lachman; it would not require submission of a suitability petition for an ANDA to simply be filed. The clinical pharmacology section of the labeling for Vibra-Tabs[®] and Doryx[®] Capsules is identical, and there is no reason why Vibra-Tabs[®] should

¹ See page 1, bottom, of suitability petition 2004P-0390, Appendix A.

not serve as the most appropriate RLD to Lachman's proposed doxycycline hyclate tablet formulation (see labeling for Vibra-Tabs[®], Appendix C; proposed labeling for the Lachman product is found in Appendix A).

There is no 75 mg tablet currently in the labeling for Vibra-Tabs[®]; however, since two suitability petitions for 75 mg tablet dosage forms of doxycycline have recently been approved (01P-0515/CP1, 01P-0109/CP1; reproduced in Appendix D), and a 50 mg doxycycline hyclate tablet was previously on the market, it should be a simple matter to submit a suitability petition requesting the addition of the 75 mg dose, with Vibra-Tabs[®] 100 mg as the RLD.

In any case, the argument by Lachman that Doryx[®] Capsules is the most suitable RLD, in [". . . an effort to make an alternate dosage form available for those individuals that either have difficulty in swallowing a capsule or who prefer a tablet dosage form as an alternative to Doryx[®] (doxycycline hyclate) Capsules (coated pellets)"], is not sensible:

- A tablet form is already available for individuals who cannot swallow capsules or who prefer a tablet;
- A tablet form of doxycycline hyclate is already available as an RLD (Vibra-Tabs[®]);
- A 50 mg doxycycline hyclate tablet was previously on the market; and
- There is no scientifically justifiable reason to use Doryx[®] Capsules as an RLD when there is a suitable tablet (Vibra-Tabs[®]) available as an RLD. The addition of a new dose (75 mg tablet) could be appropriately accomplished with a suitability petition using Vibra-Tabs[®] as the RLD.

B. The clinical pharmacology description of Doryx[®] Capsules is identical to that of Vibra-Tabs[®], so there is no reason to request a change in product formulation via the RLD;

The absorption and blood levels of doxycycline after oral administration are described in the CLINICAL PHARMACOLOGY section of both labels. Both the Doryx[®] Capsules labeling and the Vibra-Tabs[®] labeling are identical in this regard.

The argument that the "purpose of this petition is to seek the ability to file a different dosage form (tablet) that is bioequivalent to Doryx[®] (doxycycline hyclate) Capsules (coated pellets)" is not sensible in light of the fact that Vibra-Tabs[®] has identical labeling to Doryx[®] Capsules with regard to pharmacokinetic parameters.

C. The labeling provided by Lachman includes a change in dosing and administration from the labeling of Doryx[®] Capsules, without explanation, which highlights one important distinction between the capsule form and the tablet form, providing a further reason not to approve the suitability petition submitted by Lachman.

There are two errors in the labeling provided by Lachman, one typographical² and the second an omission of a section of labeling specific to the Doryx[®] Capsules (coated pellet) formulation. At the end of the Dosage and Administration (bottom of page 9 of proposed labeling, see Appendix A), Lachman has omitted a section describing that the contents of the Doryx[®] Capsules can be sprinkled in applesauce as an alternative route of administration. This section is omitted because Lachman realizes that this alternative is not possible for a tablet. This provides another noteworthy reason why substitution of a tablet for a capsule should not be permitted by the Agency, especially since the option to dose with applesauce could be important to individuals who are prescribed Doryx[®] Capsules and then receive a tablet as a pharmaceutical alternative; these patients will not be able to dose according to their doctor's instructions.

D. If FDA approves the Suitability Petition using Doryx[®] Capsules (coated doxycycline hyclate pellets) as the RLD for another doxycycline hyclate tablet, there will be a great deal of confusion on the part of patients who use and practitioners who prescribe these products.

As stated in the Preface to Approved Drug Products with Therapeutic Equivalence Evaluations (known as The Orange Book), "by designating a single reference listed drug as the standard to which all generic versions must be shown to be bioequivalent, FDA hopes to avoid possible significant variations among generic drugs and their brand name counterpart." To this end, we recommend that the most suitable RLD be chosen for the product that is the subject of the Lachman petition, which would be the RLD tablet, Vibra-Tabs[®]. Using a capsule as the RLD for a tablet is not reasonable since:

- The capsule and tablet have comparative bioavailability,
- The capsule can be administered in applesauce, which the tablet cannot,

² The footnote on page 9, Dosage and Administration section, is incorrect. After the sentence "Acute epididymo-orchitis caused by *C. trachomatis*: 100 mg, by mouth, twice-a-day for at least 10 days" should refer to reference "2," not "3."

- Substitution of a tablet as a pharmaceutical alternative form of a capsule can create confusion for both the prescriber and the patient and should be avoided, and
- There is a single RLD for a doxycycline hyclate tablet, and using a different RLD for a new doxycycline hyclate tablet will create "significant variations among generic drugs and their brand name counterpart."

This confusion would be counterproductive and against FDA's own guidelines.

III. CONCLUSION

Lachman's suitability petition, which requests that is FH Faulding Company's Doryx[®] Capsules (coated doxycycline hyclate pellets, NDA 50-582) should serve as the RLD for a new doxycycline hyclate generic tablet raises fundamental problems because there is an RLD doxycycline hyclate tablet on the market (Vibra-Tabs[®] doxycycline hyclate film coated tablets, Pfizer Labs, NDA 50-533) that would be the appropriate choice for an RLD. In addition, there are dosing differences between the proposed tablet and a Doryx[®] Capsules (i.e., administration with applesauce), while they are pharmacokinetically similar. Finally, unnecessary confusion would be created by allowing use of a capsule as an RLD to a tablet when there are already doxycycline hyclate tablets on the market. Thus, there are significant reasons against using Doryx[®] Capsules as an RLD, and a number of reasons why the RLD tablet Vibra-Tabs[®] should be the appropriate reference used for a new generic tablet being planned. Therefore, this petition must be denied.

Very truly yours,



Anthony Bruno
Executive Vice President
General Counsel

cc Gary Buehler, Director, Office of Generic Drugs

Listing of Appendices

- Appendix A. Docket No. 2004P-0390, Suitability Petition Submitted by Lachman Consultant Services, Inc. on August 31, 2004
- Appendix B. Orange Book listing for Doxycycline Hyclate
- Appendix C. Labeling for Vibra-Tabs[®] (doxycycline hyclate film coated tablets, Pfizer Labs, NDA 50-533)
- Appendix D. Docket Nos. 01P-0515/CP1 and 01P-0109/CP1