DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 50-582/S-016

F. H. Faulding & Co, Ltd.
c/o Warner Chilcott, Inc.
Attention: Alvin Howard
Vice President, Regulatory Affairs
Rockaway 80, Corporate Center
100 Enterprise Drive, Suite 280
Rockaway, NJ 07866

Dear Mr. Alvin:

Please refer to your supplemental new drug application dated January 11, 2002, received January 15, 2002, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Doryx ®(coated doxycycline hyclate pellets) Capsules. We note that this application is subject to the exemption provisions contained in section 125(d)(2) of Title I of the FDA Modernization Act of 1997.

This "Changes Being Effected" supplemental new drug application provides for revised labeling to include administration of Doryx ® for Inhalational Anthrax (Post-Exposure).

We have completed the review of this supplemental application and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon labeling text with the revisions listed below. Accordingly, the supplemental application is approved effective on the date of this letter.

1. In the WARNINGS section, insert the following 3 paragraphs, as the second, third, and fourth paragraph of the section.

   "Pseudomembranous colitis has been reported with nearly all antibacterial agents, including doxycycline, and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

   Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is a primary cause of "antibiotic-associated colitis."

   After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to discontinuation of the drug alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *Clostridium difficile* colitis."

2. In the PRECAUTIONS section, revise the *Pregnancy: Teratogenic Effects. Pregnancy Category"* and "*Nursing mothers"* subsections to read as follows.

Pregnancy: Teratogenic Effects. Pregnancy Category D:
There are no adequate and well-controlled studies on the use of doxycycline in pregnant women. The vast majority of reported experience with doxycycline during human pregnancy is short-term, first trimester exposure. There are no human data available to assess the effects of long-term therapy of doxycycline in pregnant women such as that proposed for treatment of anthrax exposure. An expert review of published data on experiences with doxycycline use during pregnancy by TERIS - the Teratogen Information System - concluded that therapeutic doses during pregnancy are unlikely to pose a substantial teratogenic risk (the quantity and quality of data were assessed as limited to fair), but the data are insufficient to state that there is no risk[3].
A case-control study (18,515 mothers of infants with congenital anomalies and 32,804 mothers of infants with no congenital anomalies) shows a weak but marginally statistically significant association with total malformations and use of doxycycline anytime during pregnancy. (Sixty-three (0.19%) of the controls and 56 (0.30%) of the cases were treated with doxycycline.) This association was not seen when the analysis was confined to maternal treatment during the period of organogenesis (i.e., in the second and third months of gestation) with the exception of a marginal relationship with neural tube defect based on only two exposed cases[4].

A small prospective study of 81 pregnancies describes 43 pregnant women treated for 10 days with doxycycline during early first trimester. All mothers reported their exposed infants were normal at 1 year of age[5].

Nursing Mothers

Tetracyclines are excreted in human milk, however, the extent of absorption of tetracyclines, including doxycycline, by the breastfed infant is not known. Short-term use by lactating women is not necessarily contraindicated; however, the effects of prolonged exposure to doxycycline in breast milk are unknown[6]. Because of the potential for adverse reactions in nursing infants from doxcycline, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. (See **WARNINGS.**)

3. Add the following references to the list of references at the end of the current label.

[3.] – Friedman JM and Polifka JE. *Teratogenic Effects of Drugs. A Resource for Clinicians (TERIS).* Baltimore, MD: The Johns Hopkins University Press: 2000: 149-195.
[4.] – Cziezel AE and Rockenbauer M. Teratogenic study of doxycycline. *Obstet Gynecol* 1997;89:524-528.
[5.] - Horne HW Jr. and Kundsin RB. The role of mycoplasma among 81 consecutive pregnancies: a prospective study. *Int J Fertil* 1980; 25:315-317.
[6.] – Hale T. *Medications and Mothers Milk.* 9th. edition. Amarillo, TX: Pharmasoft Publishing 2000; 225-226.

The final printed labeling (FPL) must be identical, and include the minor editorial revisions indicated, to the submitted draft labeling (package insert submitted January 11, 2002). These revisions are terms of the approval of this application.

Please submit the copies of final printed labeling (FPL) electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 50-582/S-016." Approval of this submission by FDA is not required before the labeling is used.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Judit Milstein, Regulatory Project Manager, at (301) 827-2207.

Sincerely,

{See appended electronic signature page}

Janice M. Soreth, M.D.
Director
Division of Anti-Infective Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Janice Soreth

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