



September 10, 2004

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

### **CITIZEN PETITION**

F H Faulding & Co. Limited t/a Mayne Pharma International and Warner Chilcott Inc. submit this petition in accordance with 21 C.F.R. § 10.20 and § 10.30 regarding the acceptance for filing, review, and approval by the Commissioner of Food and Drugs of abbreviated new drug applications ("ANDAs") for doxycycline hyclate capsule products that rely on Mayne Pharma USA's product DORYX® (coated doxycycline hyclate pellets) as the reference listed drug. The DORYX capsules contain specially coated delayed release pellets. Capsules containing doxycycline hyclate in a powder or other fill present a different clinical profile than DORYX and are not the same dosage form. Accordingly, FDA should require that an ANDA applicant for a doxycycline hyclate capsule product containing powder or other similar fill and relying on DORYX as the reference listed drug first obtain FDA's acceptance of a suitability petition for a change in dosage form. FDA should also evaluate whether there is information in any such ANDA to address the safety considerations that can arise with doxycycline hyclate formulations when coated delayed release pellets are not used.

#### ***A. Action Requested***

By this petition the undersigned requests that the Commissioner (1) confirm that capsules containing coated doxycycline hyclate pellets in a delayed release formulation are not the same dosage form as capsules containing doxycycline hyclate powder or fill other than coated pellets, (2) rule that ANDAs seeking approval of a powder filled capsule doxycycline hyclate product reference an existing NDA for such a product rather than DORYX, or alternatively require a suitability petition before accepting any ANDA for capsules without coated doxycycline hyclate pellets that relies on DORYX Capsules as the reference listed drug, (3) revoke its acceptance for filing of any ANDA submitted by Mutual Pharmaceutical Company, Inc. ("Mutual") and any other ANDA citing DORYX for a capsule dosage form of doxycycline hyclate capsules without the coated pellets which does not have an approved suitability petition, (4) ensure that any ANDA relying on DORYX presents the same clinical profile with respect to gastric irritation and nausea, and

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(5) refuse to rate any ANDAs for a doxycycline hyclate capsule with powder or fill other than delayed release coated pellets as pharmaceutically and therapeutically equivalent to DORYX.

The intention of this petition is to present the Commissioner with evidence as to why under established FDA policies DORYX Capsules containing specially coated pellets of doxycycline hyclate are a different dosage form than capsules containing doxycycline hyclate as a powder or fill other than coated pellets. Due to the differences between these two dosage forms, the petitioner further intends to demonstrate to the Commissioner why an ANDA for an oral capsule that contains doxycycline hyclate powder or other fill that is different than coated pellets should not be approved as pharmaceutically and therapeutically equivalent to DORYX Capsules, and should only be permitted to use Doryx Capsules as the reference listed drug if FDA first grants a suitability petition if at all.

In accordance with 21 CFR § 320.33, our requested actions are based on the following criteria and evidence:

- DORYX Capsules (coated doxycycline hyclate pellets) are a unique dosage form that differs from other doxycycline hyclate capsule products in that the active drug is encapsulated in specially coated pellets within the capsule dosage form.
- The specially coated pellets that contain the active drug in DORYX Capsules delay the release of the active drug in the stomach but allow release of the active drug in the small intestine.
- DORYX Capsules (coated doxycycline hyclate pellets) offer clinical advantages over capsule formulations that do not contain specially coated pellets, as evidenced by two well controlled clinical trials that compare DORYX capsules to a capsule formulation containing powder. These differences should be taken into consideration when evaluating any ANDA for doxycycline hyclate capsule products that do not contain specially coated pellets in comparison to DORYX Capsules.
- DORYX Capsules (coated doxycycline hyclate pellets) are subject to a different USP monograph than other doxycycline hyclate capsules.
- An ANDA citing DORYX Capsules would need to be pharmaceutically and therapeutically equivalent to DORYX Capsules in order to receive an AB therapeutic equivalence rating in the Orange Book. These standards are not met by a product without coated doxycycline hyclate pellets.

- DORYX Capsules are the incorrect reference product for Mutual and other such ANDA applicants to use because a powder filled capsule already exists as an NDA.

The above listed points are explained more fully below.

### ***B. Statement of Grounds***

#### **I. Background**

On February 4, 2004 Mutual filed a Citizen Petition (Docket 2004P-0054) requesting that the FDA determine that the drug product doxycycline hyclate capsules 75 mg and 100 mg are suitable for evaluation as an ANDA when the reference listed drug product for the application would be DORYX Capsules (Attachment 1). In this suitability petition, Mutual also requested a change in dosage form from the reference listed drug product, so that the ANDA would be for an oral capsule containing powder or fill other than coated pellets, rather than the "Capsule, coated pellet" dosage form that was approved for DORYX. Shortly following the submission of this citizen petition, on March 29, 2004, Mutual submitted a Letter of Withdrawal for the Citizen Petition to Docket 2004P-0054 (Attachment 2).

Mutual's letter of withdrawal states that Mutual was "contacted by a representative of the Regulatory Support Branch, Office of Generic Drugs, and informed that a suitability petition was not necessary for the change proposed in 2004P-0054/CP1." The letter further states that the representative who contacted Mutual said specifically that "there was nothing in the reference product's labeling, nor was there any other reason, which would cause the reference product to be considered differently than an oral capsule dosage form," and that "the reference product having been listed in the Orange Book as a unique dosage form did not make it unsuitable for referencing in an ANDA for an oral capsule product not containing coated pellets."

#### **II. The Uniqueness of DORYX<sup>®</sup> Capsules**

##### **1. Capsule, Coated Pellet Dosage Form**

According to the Mutual citizen petition withdrawal letter, a representative of the Regulatory Support Branch, Office of Generic Drugs, stated that there is nothing in the labeling of DORYX Capsules or any other reason that would cause DORYX Capsules to be considered different from an oral capsule dosage form of doxycycline hyclate without coated pellets. Any such statement is incorrect, and misstates the Agency's prior position as set forth in the Orange Book, the National Drug Code ("NDC") Directory, and the Center for Drug Evaluation and Research ("CDER") Data Standards Manual. As these sources all indicate, FDA recognizes DORYX coated pellet capsules as a distinct dosage form.

DORYX Capsules contain specially coated pellets of doxycycline hyclate for oral dosing. The unique encapsulated pellets offer an advantage to patients in that the special release coat has been specifically designed to delay the release of doxycycline in the stomach yet allow release in the small intestine. Using Mayne's proprietary technology, the doxycycline hyclate pellets are coated; dissolution of the coating is pH sensitive. The pH-controlled solubility of the pellet coat allows the rate of release of the active ingredient to be delayed as it moves from the lower pH of the stomach to the more basic pH in the intestines. This specialized formulation reduces gastric irritation while still allowing intestinal absorption of the active drug. The approved labeling for DORYX Capsules specifically indicates that the capsules are formulated to contain specially coated doxycycline hyclate pellets (Attachment 3).

In contrast, the proposed labeling for the Mutual ANDA as presented in the withdrawn Mutual suitability petition clearly demonstrates that it is not an ANDA for a delayed release dosage form like DORYX. That ANDA seeks approval for doxycycline hyclate powder filled capsules, and does not provide any indication that the capsules will contain coated doxycycline hyclate or provide for equivalent delayed release in any other manner. Nor does the proposed labeling provide patients with the dosing options, such as sprinkling the capsule contents on applesauce, available to DORYX users (Attachment 3).

The uniqueness of the DORYX Capsule dosage form is evidenced by the FDA-designated and approved dosage form for the drug product. FDA identifies the dosage form for DORYX in the Orange Book as "Capsule, Coated Pellets." The CDER Data Standards Manual for Dosage Forms further clarifies that "Capsule, Coated Pellets" and "Capsules" are distinct and separately designated dosage forms (Attachment 4). The definition for "Capsule, coated pellet" and "Capsule" both state that the dosage form is "[a] solid dosage form in which the drug is enclosed within either a hard or soft soluble container or 'shell' made of a suitable form of gelatin;" however, the definition for "Capsule, coated pellets" goes on specifically to state that for this particular dosage form "the drug itself is in the form of granules to which varying amounts of coating have been applied."

The NDC Trade Name Details Database also lists DORYX Capsules as a distinct dosage form -- different from other doxycycline hyclate capsule dosage forms -- and indicates that the difference affects the release profile of the active drug. The NDC Database lists the dosage form for DORYX Capsules (N 0430-0836-20: 75 mg bottles of 60 capsules as provided on the DORYX labeling) as "Capsules, Delayed Release, Pellets" (Attachment 5). The CDER Data Standards Manual similarly explains that a product in the dosage form category "Capsule, Delayed Release Pellets" is one with a capsule in which "the drug itself is in the form of granules to which enteric coating has been applied, thus delaying release of the drug until its passage into the intestines" (Attachment 4). The NDC Database and the CDER Data Standards Manual both underscore the functional rationale

for the formal distinction that FDA has drawn between ordinary capsules and those with coated, delayed release pellets.

These FDA pronouncements make clear that DORYX Capsules and doxycycline hyclate powder filled capsules are different dosage forms that cannot be regarded as the "same" as a matter of law or FDA policy. It follows, by definition, that the products are not pharmaceutical equivalents. Pharmaceutical equivalents "contain the same active ingredient(s), are of the same dosage form, route of administration and are identical in strength or concentration." Approved Products with Therapeutic Equivalence Evaluations 24<sup>th</sup> Edition ("Orange Book") Preface at vii. Accordingly, ANDAs for doxycycline hyclate powder filled capsules are not eligible for approval as therapeutically equivalent, substitutable generics to DORYX. Rather, Mutual's ANDA and applications like it seeking to reference DORYX are non-substitutable pharmaceutical alternatives and are eligible for approval as ANDAs only if the Agency has first approved a suitability petition for a change in dosage form. 21 U.S.C. § 355(j)(2)(C).

## 2. Clinical Advantage

DORYX is the only doxycycline hyclate product that contains specially coated pellets for oral dosing. These coated pellets provide for certain demonstrated clinical advantages over powder filled capsules. DORYX Capsules were specifically designed to reduce the known tendency for doxycycline to cause gastric irritation and nausea when taken on an empty stomach (nausea and vomiting have been reported in approximately one-third to one-half of patients receiving doxycycline in clinical studies). The small coated pellets in DORYX Capsules delay release in the stomach and allow release in the small intestine. By retarding the release of doxycycline in the stomach, yet allowing release in the small intestine, the potential for nausea is reduced without affecting overall absorption of the drug. As the only specially coated pelletized doxycycline product, DORYX is the only formulation to reduce the risk of stomach upset significantly (Attachment 6).

Clinical studies comparing the gastric tolerance of doxycycline hyclate capsules in two formulations -- DORYX (coated doxycycline hyclate pellets) and Vibramycin<sup>®</sup> hyclate capsules (doxycycline hyclate powder) -- have shown the clinical advantage of the DORYX coated doxycycline hyclate formulation. A study by R.S. Berger (1988) compared the incidence of gastrointestinal complaints in a three-way crossover study in healthy subjects comparing DORYX, Vibramycin, and placebo capsules given at the dose recommended in the approved product labeling. Symptoms such as absence or presence of nausea, vomiting, stomach or abdominal discomfort, and decreased appetite, were recorded by each subject. For each of these symptoms, DORYX was found to cause statistically fewer episodes than Vibramycin. Subjects treated with the Vibramycin powder filled doxycycline hyclate capsule reported significantly more symptoms than did the subjects treated with DORYX, and subjects taking Vibramycin also reported the highest incidence of moderate or severe nausea when taking the drug (Attachment 6). This study also

provided data showing that the peak time to nausea incidence occurred later with DORYX Capsules than it did with the powder filled capsule formulation. These data reflect and demonstrate the clinical significance of the fact that DORYX releases the majority of the active drug in the small intestine, whereas the powder filled capsule releases the active drug in the stomach.

A second study done by M.J. Story et al. (1991) further emphasizes the clinical advantage of the DORYX formulation. The Story study compared the nausea incidence associated with the two formulations of doxycycline hyclate, DORYX and Vibramycin. The study was a single dose double blind three-way crossover trial where subjects were assigned to one of three treatment groups, DORYX, Vibramycin or placebo. The results of the study showed that the number of subjects experiencing nausea was significantly greater with Vibramycin than it was with DORYX or placebo. This study concluded that the capsule formulation of DORYX with the delayed release doxycycline hyclate pellets had a much lower incidence of post dose nausea than the conventional powder filled capsule formulation in the Vibramycin dosage form (Attachment 7).

These data demonstrate that DORYX capsules have distinct safety advantages over powder filled capsule formulations of doxycycline hyclate, and provide direct clinical support for the need to treat capsules containing coated pellets and capsules containing powder fill as distinct dosage forms. The two dosage forms are not pharmaceutically equivalent, and the differences are manifest clinically in the Berger and Story studies.

Even assuming *arguendo* that the different capsule formulations could be considered pharmaceutically equivalent, these data demonstrate that DORYX capsules and capsules containing powder fill are not therapeutically equivalent. FDA considers drug products to be therapeutically equivalent only if they are pharmaceutically equivalent *and* can be expected to have the same clinical and safety profile under the labeled conditions. *See* Orange Book Preface at viii. In the ordinary case, therapeutic equivalence is established based upon pharmaceutical equivalence and a showing of bioequivalence. However, data from the Berger and Story studies demonstrate that powder filled doxycycline hyclate capsules cannot be expected to have the same safety profile as DORYX Capsules. These safety issues are not adequately addressed through bioequivalence data. In light of the demonstrable therapeutic differences between the coated pellets in the DORYX Capsules and powdered filled capsules such as those described in the withdrawn Mutual suitability petition, FDA should require data in addition to standard bioequivalence testing to determine whether an ANDA for a capsule formulation of doxycycline hyclate without coated pellets can be approved and rated therapeutically equivalent to DORYX. In particular, the Agency should require clinical data on nausea, vomiting, and stomach upset. Absent such data, an ANDA for doxycycline hyclate powder capsules referencing DORYX should not be approved and in no event should be rated as therapeutically equivalent to DORYX.

### 3. USP Monographs for Doxycycline Hyclate Capsule Formulations

The United States Pharmacopeia (“USP”) provides monographs for pharmaceutical dosage forms and is recognized in the FDCA as the official compendium of drug standards. Indeed, pursuant to section 501(b) of the FDCA, a drug is adulterated if “it purports to be or is represented as a drug the name of which is recognized in an official compendium, and its strength differs from or its quality or purity falls below, the standards set forth in such compendium.” 21 U.S.C. § 351(b). Thus, the preface to the Orange Book advises that an ANDA should adhere to the reference standards provided by the USP Monograph for the drug it references. It further explains (p. vii) that to be pharmaceutically equivalent, drug products must “meet the same compendial or other applicable standards (i.e., strength, quality, purity, and identity) . . . .”

The USP specifies different monographs providing different standards for “Doxycycline Hyclate Delayed Release Capsules” and “Doxycycline Hyclate Capsules” (Attachments 8 and 9). The DORYX Capsule formulation complies with the USP monograph for Doxycycline Hyclate Delayed Release Capsules. ANDAs referencing DORYX should likewise adhere to this monograph, which differs significantly from that of the Doxycycline Hyclate Capsule monograph. Any ANDA that fails to meet the same compendial standards -- the same monograph -- as DORYX Capsules is not pharmaceutically equivalent, and thus not therapeutically equivalent, to DORYX. *See* Orange Book Preface.

The USP monograph for “Doxycycline Hyclate Delayed Release Capsules” (Attachment 8) describes a two-stage method for determining drug release of the contents of the doxycycline hyclate capsules being tested. The drug release method provided in this monograph requires that the contents of the doxycycline hyclate capsule be evaluated in both an acid and a buffer medium in order to determine the amount of doxycycline dissolved at each stage. Further, the tolerances provided for each stage of dissolution testing require that in the acid stage, which tests the integrity of the coating, no individual value exceeds 50% dissolved. The monograph also requires that for capsule contents tested in a buffer stage, not less than 85% (Q) of the labeled amount of doxycycline is dissolved in 30 minutes.

The USP monograph for “Doxycycline Hyclate Capsules” (Attachment 9) differs from the monograph for Delayed Release Capsules in that the dissolution method provides one medium, water, to test the dissolution of doxycycline. The monograph also provides tolerances for the dissolution test that specify that not less than 80% of the labeled amount of doxycycline be dissolved in 30 minutes. This monograph therefore provides an entirely different set of standards to evaluate the dissolution of doxycycline than the monograph for Delayed Release Capsules. Because DORYX Capsules comply with the Doxycycline Hyclate Delayed Release Capsule monograph, ANDAs that reference DORYX Capsules

should comply with the same monograph. ANDAs that do not comply with those standards would not be pharmaceutically or therapeutically equivalent to DORYX.

### III. Meeting FDA's Established Standards for Pharmaceutical and Therapeutic Equivalence

Even if bioequivalent, an ANDA, such as Mutual's, referencing DORYX but seeking approval for a capsule containing a fill other than the doxycycline hyclate pellets found in DORYX, would not be a therapeutically equivalent, substitutable generic. Although the underlying rationale for requiring a generic product to establish bioequivalence is the assumption that "if a drug product contains a drug substance that is chemically identical and is delivered to the site of action at the same rate and extent as another drug product, then it is equivalent and can be substituted for that drug product," bioequivalence alone does not equate to therapeutic equivalence and substitutability. Orange Book Preface at ix.

For two products to be considered AB-rated therapeutic equivalents -- and thus interchangeable under many states' laws -- they must be both bioequivalent and pharmaceutically equivalent. As noted above, FDA defines drug products to be pharmaceutical equivalents if they contain the same active ingredient and are of the same dosage form, route of administration, and are identical in strength or concentration. Pharmaceutically equivalent drug products must "meet the same compendial or other applicable standards (i.e., strength, quality, purity, and identity), but they may differ in characteristics such as shape, scoring configuration, release mechanisms, packaging, excipients (including colors, flavors, preservatives), expiration time, and, within certain limits, labeling." Id. at vii.

Only ANDAs that are pharmaceutically equivalent -- are in the same dosage form and meet the same compendial standards -- to DORYX can be therapeutically equivalent and thus eligible for an "AB" rating. The dosage form listed in the Orange Book for DORYX (coated doxycycline hyclate pellets) is "Capsule, Coated Pellets." As discussed previously, this dosage form is distinct from other capsule dosage forms of doxycycline hyclate such as "Capsule" that are listed separately and defined differently in the Orange Book and elsewhere (Attachment 10). Therefore, an ANDA referencing DORYX would need to also be designated as "Capsule, Coated Pellet" in order to satisfy the FDA's definition of pharmaceutically equivalent and thus be eligible to qualify as a therapeutically equivalent, AB rated product. To be deemed therapeutically equivalent, an ANDA that lists DORYX Capsules as the reference listed drug must also meet the same compendial standards of strength, quality, purity and identity as DORYX. Otherwise the product could not secure an AB rating.

#### IV. Appropriate Reference Listed Drug for ANDAs

DORYX (coated doxycycline hyclate pellets) is not the appropriate reference product for an ANDA, such as Mutual's, seeking approval of a doxycycline hyclate capsule dosage form that is powder filled or contains other fill that is different than the coated pellets found in DORYX. A reference listed drug is the approved drug to which ANDAs are compared to show bioequivalence and on which the approval of an ANDA is based. See 21 C.F.R. § 314.94. Generally, the product in an ANDA must be the same as the reference listed drug product in the route of administration, dosage form and strength. Mutual, however, filed a petition requesting that FDA determine the suitability of DORYX as the reference listed drug for an ANDA for doxycycline hyclate capsules that are powder filled or contain other fill that is different than coated pellets.

This petition was inappropriate; not for the reasons purportedly offered by the Agency, but because a doxycycline hyclate product in the standard capsule dosage form is already approved as a reference listed drug, NDA 50007, Vibramycin. Vibramycin, marketed by Pfizer, is approved and listed in the Orange Book as an ordinary capsule dosage form for oral administration, approved in dosage strengths 50 mg and 100 mg (Attachment 11). The capsule dosage form of Vibramycin is also filled with doxycycline hyclate powder. Vibramycin would thus be the appropriate reference product for an applicant submitting an ANDA for a doxycycline hyclate capsule dosage form that is powder filled or contains fill other than coated pellets.

#### *C. Environmental Impact*

An environmental assessment report on the action requested in this petition is not required under 21 C.F.R. § 25.31.

#### *D. Economic Impact*

Pursuant to 21 C.F.R. § 10.30(b), a statement of the effect of requested action on various economic indicators will be submitted only if requested by the Commissioner.

#### *E. Certification*

The undersigned certifies that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies and representative data and information known to the petitioner which are unfavorable to the petition.

#### *F. Conclusion*

F H Faulding & Co. Limited t/a Mayne Pharma International and Warner Chilcott Inc. request that the Commissioner refrain from accepting for filing and/or approving ANDAs

filed by Mutual Pharmaceutical Inc. and others where the dosage form of the drug product that is the subject of the ANDA is "Capsule" and the reference listed drug in the ANDA is DORYX. Such ANDAs would not be pharmaceutically or therapeutically equivalent to DORYX Capsules: (1) DORYX Capsules are a unique dosage form, (2) clinical studies have shown a therapeutic difference between a capsule containing doxycycline hyclate in a powder formulation and the capsule containing doxycycline hyclate as coated pellets, reinforcing that differences between these dosage forms are important, (3) DORYX Capsules meet a different USP monograph for Doxycycline Hyclate Capsules than does a doxycycline hyclate capsule formulation that is powder filled, or contains fill other than coated pellets, and (4) DORYX is not the appropriate reference product for a powder filled capsule dosage form of doxycycline hyclate to use in an ANDA.

Sincerely,



Anthony Bruno  
Executive Vice President  
General Counsel

cc Gary Buehler, Director, Office of Generic Drugs