CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

50-795

CHEMISTRY REVIEW(S)

NDA 50-795

Doryx®
(doxycycline hyclate)
Delayed-Release Tablets

Review #1

Faulding & Co., Ltd.

Anti-Infective Drug Products

Table of Contents

Chemistry Review Data Sheet

1. NDA 50-795

2. REVIEW #: 1

3. REVIEW DATE: 8/30/04

4. REVIEWER: Rapti D. Madurawe, Ph.D.

5. PREVIOUS DOCUMENTS: None

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	05-Apr-04
Amendment	10-Jun-04
Amendment	26-Oct-04
Amendment	23-Nov-04
Amendment	10-Dec-04
Amendment	17-Dec-04
Amendment	20-Dec-04
Amendment	11-Jan-05
Amendment	18-Feb-05
Amendment	18-Mar-05
Amendment	13-Apr-05

7. NAME & ADDRESS OF APPLICANT:

Name:	F. H. Faulding & Co., Ltd (Australia) (traded as Mayne Pharma International)
Address:	1538 Main North Road Salisbury South, South Australia 5106 Australia
U.S. Representative:	Warner Chilcott, Inc. Rockaway 80 Corporate Center 100 Enterprise Drive, Suite 280 Rockaway, NJ07966 Contact: Alvin D. Howard
Telephone:	973- 442- 3233

Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:
   a) Proprietary Name: Doryx® Tablets (proposed by sponsor)
      Doryx® Delayed-Release Tablets (approved by agency)
   b) Non-Proprietary Name (USAN): coated doxycycline hyclate pellets (proposed by sponsor)
      doxycycline hyclate (approved by agency)
   c) Code Name/# (ONDC only): N/A
   d) Chem. Type/Submission Priority (ONDC only):
      - Chem. Type: 3
      - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505 (b) (1)

10. PHARMACOL. CATEGORY: Anti-infective

11. DOSAGE FORM: Delayed-Release Tablets

12. STRENGTH/POTENCY: 75 mg and 100 mg (doxycycline base)

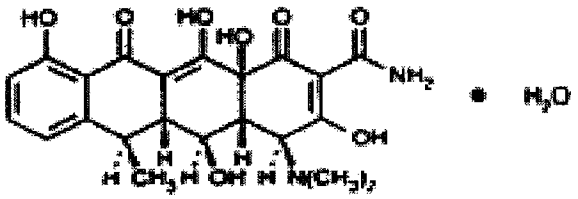
13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _X__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
    _____SPOTS product – Form Completed
    ___X___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:
    2-naphthacene-carboxamide,
    Alpha--6-desoxy-5-oxytetracycline,
    4-(Dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,5,10,12,12a-pentahydroxy-6-methyl-1,11-dioxo-, monohydrochloride, (4S, 4aR, 5S, 5aR, 6R, 12aS)-, compound with ethyl alcohol (2:1), monohydrate

    CAS Registry No.[24390-14-5]
    M.W. 512.9 M.F. $(C_{22}H_{24}N_2O_8.HCl).1/2C_2H_6O.1/2H_2O$



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
	II			1	Adequate	30-Aug-04	None
	II			1	Adequate	16-Dec-04	None
	III			1	Adequate	06-Dec-04	None
	III			1	Adequate	07-Dec-04	None
	III			1	Adequate	09-Dec-04	None
	III			7*	Adequate	07-Dec-04	Complies with 21 CFR 177.1520(C)3.2a. Food grade. USP<661>,<671> test results given in NDA.
	III			1	Adequate	07-Dec-04	None
	III			7*	Adequate	07-Dec-04	Complies with 21 CFR 177.1520(C)3.2a. Food grade. USP<661>,<671> test results given in NDA.
	III			1	Adequate	09-Dec-04	None
	III			3	Adequate	07-Jan-04	——— last reviewed and approved on 07-Jan-04. Only submission since then is an — with a list of —
	III			1	Adequate	12/9/04	None

[1] Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 –Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

* Under the new packaging guidelines, a review of plastic bottles for solid oral dosages is not required if the material is food grade and USP<661>, <671> test criteria are met.

B. Other Documents: **N/A**

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	NA		
EES	Acceptable	14-Jan-05	S. Adams
Pharm/Tox	NA		
Biopharm	NA		
LNC	NA		
Methods Validation	NA (USP)		
OPDRA	NA		
EA	NA		
Microbiology	NA		

19. COMMENTS:

NDA 50,795 was submitted by Faulding & Co., Ltd./Warner Chilcott Inc. under the title, "Doryx® (coated doxycycline hyclate pellets) Tablets, 75 mg and 100 mg". The established name and dosage form used by Faulding was not acceptable to the agency. The agency-approved name of "Doryx® (doxycycline hyclate) Delayed-Release Tablets, 75 mg and 100 mg" will be the established name of NDA 50,795 and will be thus referred to in this review.

The Chemistry review of NDA 50,795 was initially assigned to Dr. S. Pagay (HFD-520) and then re-assigned to Dr. Rapti D. Madurawe (HFD-520) on 25-Aug-04.

NDA 50,795 contains only the CMC, Biopharmacology and Labeling sections. Other review sections are referred to the applicant's approved NDA 50,582 for Doryx® Capsules and ANDA 62,653 for Doxycycline Hyclate Capsules. In Jan-05, the PDUFA due date for NDA 50,795 was extended by 3 months to 07-May-05 to accommodate new CMC and revised Biopharmacology information made available during the last few weeks of the review cycle. This review is written in the <50 page format as recommended by the Team Leader in accordance with the new ONDC CMC review guidelines. The reviewer evaluations are underlined and italicized.

The Chemistry Review for NDA 050-795

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

NDA 50,795 is recommended for approval under the product name, Doryx® (doxycycline hyclate) Delayed-Release Tablets, 75 mg and 100 mg with a 24-month product expiry when stored at 25 °C in ———————————

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

There are no Phase 4 commitments.

II. Summary of Chemistry Assessments

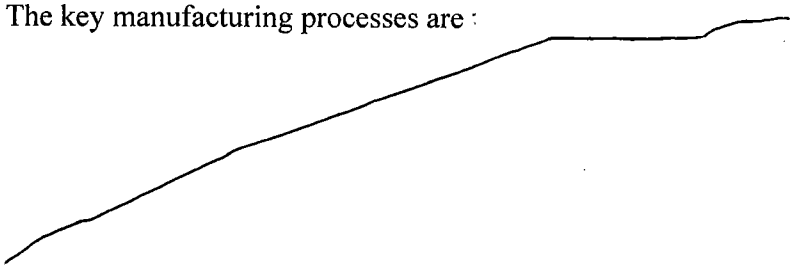
A. Description of the Drug Product(s) and Drug Substance(s)

The drug substance, doxycycline hyclate, is the hydrochloride hemiethanolate hemihydrate salt of doxycycline (the active moiety). Doxycycline belongs to the deoxytetracycline family and has been marketed for about 40 years. Doxycycline hyclate is manufactured as a light yellow, crystalline powder meeting USP monograph specifications by ———————————— ———————————The CMC is described in two established Type II DMFs which were reviewed and found to remain adequate. Both drug substance manufacturing facilities have an acceptable EES status; ——— based on profile and ——— based on inspection. There are no PAI or CMC review issues relating to the drug substance.

The drug product, Doryx® Tablets, is manufactured in two strengths, 75 mg and 100 mg of doxycycline/tablet · ———————————— by Faulding & Co. Both tablets have the same formulation and differ only by weight. The delayed-release coating is not on the tablet, but on the doxycycline hyclate pellets which are compressed to form the tablet. The pH-dependent pellet coating delays drug release until the higher pH of the small intestines is reached. The pellet formulation of Doryx® Delayed-Release Tablets differ from that of the Doryx® Capsules (delayed-release) currently marketed by the applicant.

The drug product manufacturing facility at Mayne Pharma Intl. (Faulding Pharm), Salisbury, Australia was found to be acceptable based on establishment inspection. The tablet formulation contains many excipients which are commonly used in tablet manufacture. All excipients are

compendia (USP/NF or Ph. Eur.). No potential BSE-risk material is used in the manufacture of Doryx®. The key manufacturing processes are :



As the drug substance information is provided in two DMFs with a history of "adequacy", this NDA review is primarily on the drug product. NDA information on the product components, analytical methods, impurities and container closure systems is adequate. The main weakness of this NDA is the manufacturing processes related to the delayed-release coating and compression of the pellet. Consequently, the integrity of the delayed-release coating appears to ——— over product storage. The original NDA submission contained very little drug product manufacturing process information. Further information on formulation, process and critical parameters was provided at agency request to meet the minimum acceptable standard. Although the formulation is said to be specially designed for compression of coated pellet without compromising the delayed-release action, the only supporting data provided are the final tablet dissolution data in the stability study. Accelerated – months stability data show that the amount of drug released under acidic conditions (stomach environment) increase over time. The applicant proposed different acid dissolution specification limits for product release (NMT— ,) and stability (NMT —). This was reviewed to be unacceptable as no Biopharm tolerability data was provided to support — dissolution in the stomach and the delayed-release performance of the drug should remain reasonably consistent over its storage period. Modifications were made to the pellet coating process during the review cycle. An acid dissolution specification of NMT — for both release and stability was finally accepted. The recommended drug product expiry at 25 °C storage is – months in approved bulk packaging (without retest) and – -months in approved commercial containers. The applicant has provided a stability commitment.

The product name given in the NDA is Doryx® (coated doxycycline hyclate pellets) Tablets, 75 mg and 100 mg. The established name used here is the same as that in the applicant's approved product, Doryx® Capsules. The USAN established name for the active ingredient is doxycycline hyclate. The drug product in NDA 50,795 is a delayed-release tablet. Hence, the applicant was requested to revise the product name to Doryx® (doxycycline hyclate) Delayed-Release Tablets, 75 mg and 100 mg. The applicant did not accept the revised name basing their decision on the Orange Book naming convention and their belief that coated doxycycline hyclate pellets or particles is more descriptive of the product. This name issue was referred to the DNDC

management and it was decided to base NDA approval with the product name listed as Doryx® (doxycycline hyclate) Delayed-Release Tablets, 75 mg and 100 mg.

B. Description of How the Drug Product is Intended to be Used

The drug product is orally administered for a variety of infections caused by gram-positive and negative bacteria. The actual dosage and administration is dependent on the clinical indication and is provided in the product literature.

C. Basis for Approvability or Not-Approval Recommendation

Not applicable.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

ChemistName/Date: Rapti D. Madurawe/16-Apr-05
ChemistryTeamLeader Name/Date: James Vidra
Project Manager Name/Date: Judit Milstein

C. CC Block

37 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

Withheld Track Number: Chemistry-1

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

/s/

Rapti Madurawe
4/25/05 09:53:31 AM
CHEMIST

Jim Vidra
4/25/05 10:12:05 AM
CHEMIST