CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 50-795/S-22

Trade Name:	Doryx MPC
Generic or Proper Name:	doxycycline hyclate delayed release, 60 mg and 120 mg Tablets
Sponsor:	Mayne Pharma International Pty Ltd
Approval Date:	May 20, 2016
Indication:	Rickettsial infections, Sexually transmitted infections, Respiratory tract infections, Specific bacterial infections, Ophthalmic infections, Anthrax, including inhalational anthrax (post-exposure), Alternative treatment for selected infections when penicillin is contraindicated, Adjunctive therapy in acute intestinal amebiasis and severe acne, Prophylaxis of malaria

CENTER FOR DRUG EVALUATION AND RESEARCH

NDA 50-795/S-022

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 50-795/S-22

APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 50-795/S-022

SUPPLEMENT APPROVAL

Mayne Pharma International Pty Ltd
c/o Metrics, Inc.
Attention: Susan Canady
Regulatory Affairs Specialist
1240 Sugg Parkway
Greenville, NC 27834

Dear Ms. Canady:

Please refer to your Supplemental New Drug Application (sNDA) dated July 13, 2015, received July 20, 2015, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Doryx MPC (doxycycline hyclate delayed-release) 60 mg and 120 mg Tablets.

This Prior Approval supplemental new drug application provides for a modified formulation and two new product strengths (60 mg and 120 mg tablets).

APPROVAL & LABELING

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling text for the package insert with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that includes labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

CARTON AND IMMEDIATE CONTAINER LABELS

We acknowledge your May 18, 2016 submission containing final printed carton and container labels.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Eva Zuffova, Regulatory Project Manager, at (301) 796- 0697.

Sincerely,

{See appended electronic signature page}

Sumathi Nambiar, MD, MPH
Director
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

ENCLOSURES:
Content of Labeling
Carton and Container Labeling

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

/s/

SUMATHI NAMBIAR
05/20/2016

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 50-795/S-22

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use DORYX MPC safely and effectively. See full prescribing information for DORYX MPC

DORYX MPC (doxycycline hyclate delayed-release tablets), for oral use.
Initial U.S. Approval: 1967

----------RECENT MAJOR CHANGES----------

----------INDICATIONS AND USAGE----------
Doryx MPC is a tetracycline class drug indicated for:
- Rickettsial infections (1.1)
- Sexually transmitted infections (1.2)
- Respiratory tract infections(1.3)
- Specific bacterial infections (1.4)
- Ophthalmic infections (1.5)
- Anthrax, including inhalational anthrax (post-exposure) (1.6)
- Alternative treatment for selected infections when penicillin is contraindicated (1.7)
- Adjunctive therapy in acute intestinal amebiasis and severe acne (1.8)
- Prophylaxis of malaria (1.9)

To reduce the development of drug-resistant bacteria and maintain the effectiveness of doxycycline hyclate, Doryx MPC and other antibacterial drugs, Doryx MPC Tablets should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria. (1.10)

----------DOSAGE AND ADMINISTRATION----------

- Important Administration Instructions:
  - Doryx MPC is not substitutable on a mg per mg basis with other oral doxycyclines. (2.1)
  - Do not chew or crush tablets. (2.1)
- Dosage in Adults
  - The usual dosage of Doryx MPC is 240 mg on the first day of treatment (administered 120 mg every 12 hours) followed by a maintenance dose of 120 mg daily.(2.3)
  - In the management of more severe infections (particularly chronic infections of the urinary tract), 120 mg every 12 hours is recommended. (2.3)
- Dosage in Pediatric Patients
  - For all pediatric patients weighing less than 45 kg with severe or life threatening infections (e.g., anthrax, Rocky Mountain spotted fever), the recommended dosage of Doryx MPC is 2.6 mg per kg of body weight administered every 12 hours. Pediatric patients weighing 45 kg or more should receive the adult dose.(2.3)
  - For pediatric patients with less severe disease (greater than 8 years of age and weighing less than 45 kg), the recommended dosage schedule of Doryx MPC is 5.3 mg per kg of body weight divided into two doses on the first day of treatment, followed by a maintenance dose of 2.6 mg per kg of body weight (given as a single daily dose or divided into twice daily doses). For pediatric patients weighing over 45 kg, the usual adult dose should be used.(2.3)
- See Full Prescribing Information for additional indication specific dosage information and important administration instructions for Doryx MPC. (2.3, 2.5, 2.6)

----------DOSAGE FORM AND STRENGTHS----------
Doryx MPC Delayed-Release Tablets: 60 mg, 120 mg (3)

----------CONTRAINDICATIONS----------
Doxycycline is contraindicated in persons who have shown hypersensitivity to any of the tetracyclines. (4)

----------WARNINGS AND PRECAUTIONS----------
- The use of drugs of the tetracycline-class during tooth development (last half of pregnancy, infancy and childhood to the age of 8 years) may cause permanent discoloration of the teeth (yellow-gray-brown). (5.1)
- *Clostridium difficile*-associated diarrhea. Evaluate patients if diarrhea occurs. (5.2)
- Photosensitivity manifested by an exaggerated sunburn reaction has been observed in some individuals taking tetracyclines. Limit sun exposure. (5.3)
- Overgrowth of non-susceptible organisms, including fungi, may occur. If such infections occur, discontinue use and institute appropriate therapy. (5.4)

----------ADVERSE RECTIONS----------
Adverse reactions observed in patients receiving tetracyclines include anorexia, nausea, vomiting, diarrhea, rash, photosensitivity, urticaria, and hemolytic anemia. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Mayne Pharma at 1-844-825-8500 or FDA at 1-800-FDA-1088 or www fda.gov/medwatch.

----------DRUG INTERACTIONS----------
- Patients who are on anticoagulant therapy may require downward adjustment of their anticoagulant dosage (7.1)
- Avoid co-administration of tetracyclines with penicillin (7.2)
- Absorption of tetracyclines, including Doryx MPC is impaired by antacids containing aluminum, calcium, or magnesium, bismuth subsalicylate and iron-containing preparations (7.3)
- Concurrent use of tetracyclines, including Doryx MPC may render oral contraceptives less effective (7.4)
- Barbiturates, carbamazepine, and phenytoin decrease the half-life of doxycycline (7.5)

----------USE IN SPECIFIC POPULATIONS----------
- Tetracycline-class drugs can cause fetal harm when administered to a pregnant woman, but data for doxycycline are limited. (5.6, 8.1)
- Tetracyclines are excreted in human milk; however, the extent of absorption of doxycycline in the breastfed infant is not known. Doryx MPC use during nursing should be avoided if possible. (8.3)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 5/2016

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Rickettsial Infections

Doryx MPC is indicated for treatment of Rocky Mountain spotted fever, typhus fever and the typhus group, Q fever, rickettsialpox, and tick fevers caused by *Rickettsiae*.

1.2 Sexually Transmitted Infections

Doryx MPC is indicated for treatment of the following sexually transmitted infections:

- Uncomplicated urethral, endocervical or rectal infections in adults caused by *Chlamydia trachomatis.*
- Nongonococcal urethritis caused by *Ureaplasma urealyticum*.
- Lymphogranuloma venereum caused by *Chlamydia trachomatis*.
- Granuloma inguinale caused by *Klebsiella granulomatis*.
- Uncomplicated gonorrhea caused by *Neisseria gonorrhoeae*.
- Chancroid caused by *Haemophilus ducreyi*.

1.3 Respiratory Tract Infections

Doryx MPC is indicated for treatment of the following respiratory tract infections:

- Respiratory tract infections caused by *Mycoplasma pneumoniae*.
- Psittacosis (ornithosis) caused by *Chlamydophila psittaci*.
- Because many strains of the following groups of microorganisms have been shown to be resistant to doxycycline, culture and susceptibility testing are recommended.
- Doxycycline is indicated for treatment of infections caused by the following microorganisms, when bacteriological testing indicates appropriate susceptibility to the drug:
- Respiratory tract infections caused by *Haemophilus influenzae*.
- Respiratory tract infections caused by *Klebsiella* species.
- Upper respiratory infections caused by *Streptococcus pneumoniae*.

1.4 Specific Bacterial Infections

Doryx MPC is indicated for treatment of the following specific bacterial infections:

- Relapsing fever due to *Borrelia recurrentis*.
- Plague due to *Yersinia pestis*.
- Tularemia due to *Francisella tularensis*.
- Cholera caused by *Vibrio cholerae*.
- Campylobacter fetus infections caused by *Campylobacter fetus*.
- Brucellosis due to *Brucella* species (in conjunction with streptomycin).
- Bartonellosis due to *Bartonella bacilliformis*.

Because many strains of the following groups of microorganisms have been shown to be resistant to doxycycline, culture and susceptibility testing are recommended.

Doryx MPC is indicated for treatment of infections caused by the following gram-negative microorganisms, when bacteriological testing indicates appropriate susceptibility to the drug:

- *Escherichia coli*
- *Enterobacter aerogenes*
- *Shigella* species
- *Acinetobacter* species
- Urinary tract infections caused by *Klebsiella* species.

1.5 Ophthalmic Infections

Doryx MPC is indicated for treatment of the following ophthalmic infections:

- Trachoma caused by *Chlamydia trachomatis*, although the infectious agent is not always eliminated as judged by immunofluorescence.
- Inclusion conjunctivitis caused by *Chlamydia trachomatis*.

1.6 Anthrax Including Inhalational Anthrax (Post-Exposure)

Doryx MPC is indicated for treatment of Anthrax due to *Bacillus anthracis*, including inhalational anthrax (post-exposure): to reduce the incidence or progression of disease following exposure to aerosolized *Bacillus anthracis*.

1.7 Alternative Treatment for Selected Infections when Penicillin is Contraindicated

Doryx MPC is indicated as an alternative treatment for the following selected infections when penicillin is contraindicated:

- Syphilis caused by *Treponema pallidum*.

- Yaws caused by *Treponema pallidum* subspecies *pertenue*.
- Listeriosis due to *Listeria monocytogenes*.
- Vincent's infection caused by *Fusobacterium fusiforme.*
- Actinomycosis caused by *Actinomyces israelii*.
- Infections caused by *Clostridium* species.

1.8 Adjunctive Therapy for Acute Intestinal Amebiasis and Severe Acne

In acute intestinal amebiasis, Doryx MPC may be a useful adjunct to amebicides.

In severe acne, Doryx MPC may be useful adjunctive therapy.

1.9 Prophylaxis of Malaria

Doryx MPC is indicated for the prophylaxis of malaria due to *Plasmodium falciparum* in short-term travelers (less than 4 months) to areas with chloroquine and/or pyrimethamine-sulfadoxine resistant strains [*see Dosage and Administration (2.2) and Patient Counseling Information (17)*].

1.10 Usage

To reduce the development of drug-resistant bacteria and maintain the effectiveness of Doryx MPC and other antibacterial drugs, Doryx MPC should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

2 DOSAGE AND ADMINISTRATION

2.1 Important Dosage and Administration Instructions

- DORYX MPC is not substitutable on a mg per mg basis with other oral doxycyclines. To avoid prescribing errors, do not substitute Doryx MPC for other oral doxycyclines on a mg per mg basis because of differing bioavailability.
- Do not chew or crush tablets.
- The recommended dosage, frequency of administration and weight-based dosage recommendations of DORYX MPC differ from that of the other tetracyclines [*see Dosage and Administration (2.2, 2.3, 2.4)*]. Exceeding the recommended dosage may result in an increased incidence of adverse reactions.
- Administer DORYX MPC with an adequate amount of fluid to wash down the drug and reduce the risk of esophageal irritation and ulceration [*see Adverse Reactions (6.1)*].

2.2 Switching from DORYX to Doryx MPC

When switching from DORYX to DORYX MPC*:*

- A 60 mg dose of DORYX MPC will replace a 50 mg dose of DORYX
- A 120 mg dose of DORYX MPC will replace a 100 mg dose of DORYX.

2.3 Dosage in Adults Patients

- The usual dosage of DORYX MPC is 240 mg on the first day of treatment (administered 120 mg every 12 hours) followed by a maintenance dose of 120 mg daily. The maintenance dose may be administered as a single dose or as 60 mg every 12 hours.
- In the management of more severe infections (particularly chronic infections of the urinary tract), 120 mg every 12 hours is recommended.
- For certain selected specific indications, the recommended duration or dosage and duration of DORYX MPC in adult patients are as follows:

1. Streptococcal infections, therapy should be continued for 10 days.
2. Uncomplicated urethral, endocervical, or rectal infection caused by *C. trachomatis*: 120 mg by mouth twice-a-day for 7 days.
3. Uncomplicated gonococcal infections in adults (except anorectal infections in men): 120 mg, by mouth, twice-a-day for 7 days. As an alternate single visit dose, administer 360 mg followed in one hour by a second 360 mg dose.
4. Nongonococcal urethritis (NGU) caused by *C. trachomatis* and *U. urealyticum*: 120 mg by mouth twice a day for 7 days.
5. Syphilis – early: Patients who are allergic to penicillin should be treated with doxycycline 120 mg by mouth twice-a-day for 2 weeks.
6. Syphilis of more than one year's duration: Patients who are allergic to penicillin should be treated with doxycycline 120 mg by mouth twice-a-day for 4 weeks.
7. Acute epididymo-orchitis caused by *N. gonorrhoeae*: 120 mg by mouth, twice-a-day for at least 10 days.
8. Acute epididymo-orchitis caused by *C. trachomatis*: 120 mg, by mouth, twice-a-day for at least 10 days

2.4 Dosage in Pediatric Patients

- For all pediatric patients weighing less than 45 kg with severe or life threatening infections (e.g., anthrax, Rocky Mountain spotted fever), the recommended dosage of Doryx MPC is 2.6 mg per kg of body weight administered every 12 hours. Pediatric patients weighing 45 kg or more should receive the adult dose *[see Warnings and Precautions (5.1)]*.
- For pediatric patients with less severe disease (greater than 8 years of age and weighing less than 45 kg), the recommended dosage schedule of Doryx MPC

is 5.3 mg per kg of body weight divided into two doses on the first day of treatment, followed by a maintenance dose of 2.6 mg per kg of body weight (given as a single daily dose or divided into twice daily doses). For pediatric patients weighing over 45 kg, the usual adult dose should be used.

2.5 Dosage for Prophylaxis of Malaria

For adults, the recommended dose of Doryx MPC is 120 mg daily.

For pediatric patients 8 years of age and older, the recommended dosage of Doryx MPC is 2.4 mg per kg of body weight administered once daily. Pediatric patients weighing 45 kg or more should receive the adult dose.

Prophylaxis should begin 1 or 2 days before travel to the malarious area. Prophylaxis should be continued daily during travel in the malarious area and for 4 weeks after the traveler leaves the malarious area.

2.6 Dosage for Inhalational Anthrax (Post-Exposure)

For adults, the recommended dosage is 120 mg, of Doryx MPC, by mouth, twice-a-day for 60 days.

For pediatric patients weighing less than 45 kg, the recommended dosage of Doryx MPC is 2.6 mg per kg of body weight, by mouth, twice-a-day for 60 days. Pediatric patients weighing 45 kg or more should receive the adult dose.

3 DOSAGE FORMS AND STRENGTHS

Doryx MPC (doxycycline hyclate delayed-release tablets), 60 mg and 120 mg are white, oval tablets containing yellow pellets and debossed on one face with "D6" and "DC", respectively, and plain on the other. Each tablet contains doxycycline 60 mg or 120 mg (equivalent to doxycycline hyclate 69.4 mg or 138.8 mg).

4 CONTRAINDICATIONS

Doryx MPC is contraindicated in persons who have shown hypersensitivity to any of the tetracyclines.

5 WARNINGS AND PRECAUTIONS

5.1 Tooth Development

The use of drugs of the tetracycline-class during tooth development (last half of pregnancy, infancy and childhood to the age of 8 years) may cause permanent discoloration of the teeth (yellow-gray-brown). This adverse reaction is more common during long-term use of the drugs but it has been observed following repeated short-term courses. Enamel hypoplasia has also been reported. Use Doryx MPC in pediatric patients 8 years of age or less only when the potential benefits are expected to outweigh the risks in severe or life-threatening conditions (e.g., anthrax, Rocky Mountain spotted fever), particularly when there are no alternative therapies.

5.2 Clostridium difficile Associated Diarrhea

Clostridium difficile associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including Doryx MPC Tablets, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile*.

C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibacterial use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, ongoing antibacterial use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibacterial treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.

5.3 Photosensitivity

Photosensitivity manifested by an exaggerated sunburn reaction has been observed in some individuals taking tetracyclines. Patients apt to be exposed to direct sunlight or ultraviolet light should be advised that this reaction can occur with tetracycline drugs, and treatment should be discontinued at the first evidence of skin erythema.

5.4 Potential for Microbial Overgrowth

Doryx MPC may result in overgrowth of non-susceptible organisms, including fungi. If such infections occur, discontinue use and institute appropriate therapy.

5.5 Intracranial Hypertension

Intracranial hypertension (IH, pseudotumor cerebri) has been associated with the use of tetracycline including Doryx MPC. Clinical manifestations of IH include headache, blurred vision, diplopia, and vision loss; papilledema can be found on fundoscopy. Women of childbearing age who are overweight or have a history of IH are at greater risk for developing tetracycline associated IH. Avoid concomitant use of isotretinoin and Doryx MPC because isotretinoin is also known to cause pseudotumor cerebri.

Although IH typically resolves after discontinuation of treatment, the possibility for permanent visual loss exists. If visual disturbance occurs during treatment, prompt ophthalmologic evaluation is warranted. Since intracranial pressure can remain elevated for weeks after drug cessation patients should be monitored until they stabilize.

5.6 Skeletal Development

All tetracyclines form a stable calcium complex in any bone-forming tissue. A decrease in fibula growth rate has been observed in prematures given oral tetracycline in doses of 25 mg/kg every six hours. This reaction was shown to be reversible when the drug was discontinued. [*See Use in Specific Populations (8.1)*].

5.7 Antianabolic Action

The antianabolic action of the tetracyclines may cause an increase in BUN. Studies to date indicate that this does not occur with the use of doxycycline in patients with impaired renal function.

5.8 Malaria

Doxycycline offers substantial but not complete suppression of the asexual blood stages of *Plasmodium* strains.

Doxycycline does not suppress *P. falciparum's* sexual blood stage gametocytes. Subjects completing this prophylactic regimen may still transmit the infection to mosquitoes outside endemic areas.

5.9 Development of Drug-Resistant Bacteria

Prescribing Doryx MPC in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

5.10 Laboratory Monitoring for Long-Term Therapy

In long-term therapy, periodic laboratory evaluation of organ systems, including hematopoietic, renal, and hepatic studies should be performed.

6 ADVERSE REACTIONS

The following adverse reactions have been identified during post-approval use of doxycycline. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Due to oral doxycycline's virtually complete absorption, side effects to the lower bowel, particularly diarrhea, have been infrequent. The following adverse reactions have been observed in patients receiving tetracyclines:

Gastrointestinal: Anorexia, nausea, vomiting, diarrhea, glossitis, dysphagia, enterocolitis, and inflammatory lesions (with monilial overgrowth) in the anogenital region. Hepatotoxicity has been reported. These reactions have been caused by both the oral and parenteral administration of tetracyclines. Esophagitis and esophageal ulcerations have been reported in patients receiving capsule and tablet forms of drugs in the tetracycline-class. Most of these patients took medications immediately before going to bed [*see Dosage and Administration (2.1)*].

Skin: Maculopapular and erythematous rashes, Stevens-Johnson syndrome, toxic epidermal necrolysis, exfoliative dermatitis, and erythema multiforme have been reported. Photosensitivity is discussed above [*see Warnings and Precautions (5.3)*].

Renal: Rise in BUN has been reported and is apparently dose-related [*see Warnings and Precautions (5.7)*].

Hypersensitivity reactions: Urticaria, angioneurotic edema, anaphylaxis, anaphylactoid purpura, serum sickness, pericarditis, and exacerbation of systemic lupus erythematosus.

Blood: Hemolytic anemia, thrombocytopenia, neutropenia, and eosinophilia have been reported.

Intracranial Hypertension: Intracranial hypertension (IH, pseudotumor cerebri) has been associated with the use of tetracycline [*See Warnings and Precautions (5.5)*]

Thyroid Gland Changes: When given over prolonged periods, tetracyclines have been reported to produce brown-black microscopic discoloration of thyroid glands. No abnormalities of thyroid function are known to occur.

7 DRUG INTERACTIONS

7.1 Anticoagulant Drugs

Because tetracyclines have been shown to depress plasma prothrombin activity, patients who are on anticoagulant therapy may require downward adjustment of their anticoagulant dosage.

7.2 Penicillin

Since bacteriostatic drugs may interfere with the bactericidal action of penicillin, it is advisable to avoid giving tetracyclines, including Doryx MPC in conjunction with penicillin.

7.3 Antacids and Iron Preparations

Absorption of tetracyclines including Doryx MPC is impaired by antacids containing aluminum, calcium, or magnesium, bismuth subsalicylate, and iron-containing preparations.

7.4 Oral Contraceptives

Concurrent use of tetracyclines, including Doryx MPC may render oral contraceptives less effective.

7.5 Barbiturates and anti-epileptics

Barbiturates, carbamazepine, and phenytoin decrease the half-life of doxycycline.

7.6 Penthrane

The concurrent use of tetracycline and Penthrane® (methoxyflurane) has been reported to result in fatal renal toxicity.

7.7 Drug/Laboratory Test Interactions

False elevations of urinary catecholamines may occur due to interference with the fluorescence test.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no adequate 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 the 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.[1] In the U.S. general population the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively [*see Data*].

Clinical Considerations

Embryo/Fetal Risk

Results of animal studies indicate that tetracyclines cross the placenta, are found in fetal tissues, and can have toxic effects on the developing fetus (often related to retardation of skeletal development). Evidence of embryotoxicity also has been noted in animals treated early in pregnancy. If any tetracycline is used during pregnancy or if the patient becomes pregnant while taking these drugs, the patient should be apprised of the potential hazard to the fetus. [*see Warnings and Precautions (5.1, 5.6)*].

Data

Human Data

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.[2]

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.[3]

8.2 Lactation

Risk Summary

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 contraindicated. The effects of prolonged exposure to doxycycline on breast milk production and breast fed neonates, infants and children are unknown.[4] The developmental and health benefits of breast feeding should be considered along with the mother's clinical need for Doryx MPC and any potential adverse effects on the breast fed child from Doryx MPC or from the underlying maternal condition [*see Warnings and Precautions (5.1, 5.6)*].

8.4 Pediatric Use

Because of the effects of drugs of the tetracycline-class on tooth development and growth, use Doryx MPC in pediatric patients 8 years of age or less only when the potential benefits are expected to outweigh the risks in severe or life-threatening conditions (e.g., anthrax, Rocky Mountain spotted fever), particularly when there are no alternative therapies [*see Warnings and Precautions (5.1, 5.6) and Dosage and Administration (2.1, 2.44)*].

8.5 Geriatric Use

Clinical studies of Doryx MPC did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. Doryx MPC Tablets each contains less than 10 mg of sodium.

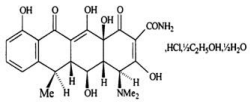
10 OVERDOSAGE

In case of overdosage, discontinue medication, treat symptomatically and institute supportive measures. Dialysis does not alter serum half-life and thus would not be of benefit in treating cases of overdosage.

11 DESCRIPTION

Doryx MPC (doxycycline hyclate delayed-release tablets) for oral use, contain doxycycline hyclate, a tetracycline class drug synthetically derived from oxytetracycline, in a delayed-release formulation consisting of pellets with a modified polymer enteric coat that has increased acid resistance.

The structural formula for doxycycline hyclate is:



with a molecular formula of $C_{22}H_{24}N_2O_8$, HCl, ½ C_2H_6O, ½ H_2O and a molecular weight of 512.9 The chemical name for doxycycline hyclate is [4S(4aR,5S,5aR,6R,12aS)]-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,5,10,12,12a-pentahydroxy-6-methyl-1,11-deoxonaphthacene-2-carboxamide monohydrochloride, compound with ethyl alcohol (2:1), monohydrate. Doxycycline hyclate is a yellow crystalline powder soluble in water and in solutions of alkali hydroxides and carbonates. Doxycycline has a high degree of lipid solubility and a low affinity for calcium binding. It is highly stable in normal human serum. Doxycycline will not degrade into an epianhydro form.

Each tablet contains doxycycline 60 mg or 120 mg (equivalent to doxycycline hyclate 69.4 mg or 138.8 mg). Inactive ingredients in the tablet formulation are: lactose monohydrate; microcrystalline cellulose; sodium lauryl sulfate; sodium chloride; talc, anhydrous lactose; corn starch; crospovidone; magnesium stearate; cellulosic polymer coating.

Each Doryx MPC 60 mg Tablet contains 3.6 mg (0.157 mEq) of sodium and each Doryx MPC 120 mg Tablet contains 7.2 mg (0.313 mEq) of sodium.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Doxycycline is a tetracycline-class antimicrobial drug [*see Microbiology (12.4)*].

12.3 Pharmacokinetics

Absorption

Following administration of a single dose of Doryx MPC under fasting conditions, the AUCinf and Cmax were 26.7 mcg-h/mL and 1.6 mcg//mL, respectively. The Tmax was 2.8 hours. In a single-dose study to evaluate the relative bioavailability in healthy adult subjects under fasted conditions, Doryx MPC 120 mg Tablets was found to be bioequivalent to Doryx 100 mg tablets..

Excretion

Tetracyclines are concentrated in bile by the liver and excreted in the urine and feces at high concentrations and in a biologically active form. Excretion of doxycycline by the kidney is about 40%/72 hours in individuals with a creatinine clearance of about 75 mL/min. This percentage may fall as low as 1-5%/72 hours in individuals with a creatinine clearance below 10 mL/min.

Studies have shown no significant difference in the serum half-life of doxycycline (range 18 to 22 hours) in individuals with normal and severely impaired renal function. Hemodialysis does not alter the serum half-life.

12.4 Microbiology

Mechanism of Action

Doxycycline inhibits bacterial protein synthesis by binding to the 30S ribosomal subunit. Doxycycline has bacteriostatic activity against a broad range of Gram-positive and Gram-negative bacteria.

Resistance

Cross-resistance between tetracyclines is common.

Antimicrobial Activity

Doxycycline has been shown to be active against most isolates of the following bacteria, both *in vitro* and in clinical infections [see *Indications and Usage (1)*].

Gram-negative Bacteria

Acinetobacter species
Bartonella bacilliformis
Brucella species
Campylobacter fetus
Enterobacter aerogenes
Escherichia coli
Francisella tularensis
Haemophilus ducreyi
Haemophilus influenzae
Klebsiella granulomatis
Klebsiella species
Neisseria gonorrhoeae
Shigella species
Vibrio cholerae

Yersinia pestis

Gram-positive Bacteria
Bacillus anthracis
Listeria monocytogenes
Streptococcus pneumoniae

Anerobic Bacteria
Clostridium species
Fusobacterium fusiforme
Propionibacterium acnes

Other Bacteria
Borrelia recurrentis
Chlamydophila psittaci
Chlamydia trachomatis
Mycoplasma pneumonia
Norcardiae and other aerobic *Actinomyces* species
Rickettsiae
Treponema pallidum
Treponema pallidum subspecies *pertenue*
Ureaplasma urealyticum

Parasites
Balantidium coli
Entamoeba species
*Plasmodium falciparum**
*Doxycycline has been found to be active against the asexual erythrocytic forms of *Plasmodium falciparum* but not against the gametocytes of *P. falciparum.* The precise mechanism of action of the drug is not known.

Susceptibility Test Methods

When available, the clinical microbiology laboratory should provide cumulative reports of *in vitro* susceptibility test results for antibacterial drugs used in local hospitals and practice areas to the physician as periodic reports that describe the susceptibility profile of nosocomial and community-acquired pathogens. These reports should aid the physician in selecting an antibacterial drug for treatment.

Dilution Techniques

Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized test method (broth and/or agar).[5,6,8] The MIC values should be interpreted according to the criteria provided in Table 1.

Diffusion Techniques

Quantitative methods that require measurement of zone diameters can also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. The zone size should be determined using a standard test method.[5,7,8] This procedure uses paper disks impregnated with 30 mcg doxycycline to test the susceptibility of bacteria to doxycycline. The disk diffusion interpretive criteria are provided in Table 1.

Anaerobic Techniques

For anaerobic bacteria the susceptibility to doxycycline can be determined by a standardized test method.[5,9] The MIC values obtained should be interpreted according to the criteria provided in Table 1.

Table 1: Susceptibility Test Interpretive Criteria for Doxycycline and Tetracycline

Bacteria[a]	Minimal Inhibitory Concentration (mcg/mL)			Zone Diameter (mm)			Agar Dilution (mcg/mL)		
	S	I	R	S	I	R	S	I	R
Acinetobacter spp,									
Doxycycline	≤4	8	≥16	≥13	10-12	≤9	-	-	-
Tetracycline	≤4	8	≥16	≥15	12-14	≤11	-	-	-
Anaerobes									
Tetracycline	-	-	-	-	-	-	≤4	8	≥16
Bacillus anthracis[ab]									
Doxycycline	≤1	-	-	-	-	-	-	-	-
Tetracycline	≤1	-	-	-	-	-	-	-	-
Brucella species[ab]									
Doxycycline	≤1	-	-	-	-	-	-	-	-
Tetracycline	≤1	-	-	-	-	-	-	-	-
Enterobacteriaceae									
Doxycycline	≤4	8	≥16	≥14	11-13	≤10	-	-	-
Tetracycline	≤4	8	≥16	≥15	12-14	≤11	-	-	-
FranciscеIIa tularensis[ab]									
Doxycycline	≤4	-	-	-	-	-	-	-	-
Tetracycline	≤4	-	-	-	-	-	-	-	-
Haemophilus influenzae									
Tetracycline	≤2	4	≥8	≥29	26-28	≤25	-	-	-
Mycoplasma pneumoniae									
Tetracycline	-	-	-	-	-	-	≤2	-	-
Nocardiae and other aerobic *Actinomyces* species[ab]									
Doxycycline	≤1	2-4	≥8						
Neisseria gonorrhoeae[c]									
Tetracycline	-	-	-	≥38	31-37	≤30	≤0.25	0.5-1	≥2
Streptococcus pneumoniae									
Doxycycline	≤0.25	0.5	≥1	≥28	25-27	≤24	-	-	-
Tetracycline	≤1	2	≥4	≥28	25-27	≤24	-	-	-
Vibrio cholerae									
Doxycycline	≤4	8	≥16	-	-	-	-	-	-
Tetracycline	≤4	8	≥16	-	-	-	-	-	-
Yersinia pestis									
Doxycycline	≤4	8	≥16	-	-	-	-	-	-
Tetracycline	≤4	8	≥16	-	-	-	-	-	-
UreaPlasma urealyticum									
Tetracycline	-	-	-	-	-	-	≤1	-	≥2

[a]Organisms susceptible to tetracycline are also considered susceptible to doxycycline, However, some organisms that are intermediate or resistant to tetracycline may be susceptible to doxycycline.

[b]The current absence of resistance isolates precludes defining any results other than "Susceptible". If isolates yielding MIC results other than susceptible, they should be submitted to a reference laboratory for further testing.

[c]Gonococci with 30 mcg tetracycline disk zone diameters of less than 19 mm usually indicate a plasmid-mediated tetracycline resistant *N. gonorrhoeae* isolate. Resistance in these strains should be confirmed by a dilution test (MIC greater than or equal to 16 mcg/mL).

A report of *Susceptible* (S) indicates that the antimicrobial is likely to inhibit growth of the microorganism if the antimicrobial drug reaches the concentration usually achievable at the site of infection. A report of *Intermediate* (I) indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone that prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of *Resistant* (R) indicates that the antimicrobial drug is not likely to inhibit growth of the microorganism if the antimicrobial drug reaches the concentrations usually achievable at the infection site; other therapy should be selected.

Quality Control

Standardized susceptibility test procedures require the use of laboratory controls to monitor and ensure the accuracy and precision of the supplies and reagents used in the assay, and the techniques of the individuals performing the test.[5,6,7,8,9,10,11] Standard doxycycline and tetracycline powders should provide the following range of MIC values noted in Table 2. For the diffusion technique using the 30 mcg doxycycline disk the criteria noted in Table 2 should be achieved.

Table 2: Acceptable Quality Control Ranges for Susceptibility Testing for Doxycycline and Tetracycline

QC Strain	Minimal Inhibitory Concentration (mcg/mL)	Zone Diameter (mm)	Agar Dilution (mcg/mL)
Enterococcus faecalis ATCC 29212 Doxycycline Tetracycline	 2-8 8-32	 - -	 - -
Escherichia coli ATCC 25922 Doxycycline Tetracycline	 0.5-2 0.5-2	 18-24 18-25	 - -
Eubacterium lentum ATCC 43055 Doxycycline	 2 - 16	 -	 -
Haemophilus influenzae ATCC 49247 Tetracycline	 4-32	 14-22	 -
Neisseria gonorrhoeae ATCC 49226 Tetracycline	 -	 30-42	 0.25-1
Staphylococcus aureus ATCC 25923 Doxycycline Tetracycline	 - -	 23-29 24-30	 - -
Staphylococcus aureus ATCC 29213 Doxycycline Tetracycline	 0.12-0.5 0.12-1		 - -
StaphyIococcus pneumoniae ATCC 49619 Doxycycline Tetracycline	 0.015-0.12 0.06-0.5	 25-34 27-31	 - -
Bacteroides fragiIis ATCC 25285 Tetracycline	 -	 -	 0.125-0.5
Bacteroides thetaiotaomicron ATCC 29741 Doxycycline Tetracycline	 2 - 8 -	 - -	 - 8-32
Mycoplasma pneumoniae ATCC 29342 Tetracycline	 0.06-0.5	 -	 0.06-0.5
Ureaplasma urealyticum ATCC 33175 Tetracycline	 -	 -	 ≥8

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals to evaluate carcinogenic potential of doxycycline have not been conducted. However, there has been evidence of oncogenic activity in rats in studies with the related antibiotics, oxytetracycline (adrenal and pituitary tumors) and minocycline (thyroid tumors). Likewise, although mutagenicity studies of doxycycline have not been conducted, positive results in *in vitro* mammalian cell assays have been reported for related antibacterials (tetracycline, oxytetracycline).

Doxycycline administered orally at dosage levels as high as 250 mg/kg/day had no apparent effect on the fertility of female rats. Effect on male fertility has not been studied.

13.2 Animal Toxicology and/or Pharmacology

Hyperpigmentation of the thyroid has been produced by members of the tetracycline-class in the following species: in rats by oxytetracycline, doxycycline, tetracycline PO_4, and methacycline; in minipigs by doxycycline, minocycline, tetracycline PO_4, and methacycline; in dogs by doxycycline and minocycline; in monkeys by minocycline.

Minocycline, tetracycline PO_4, methacycline, doxycycline, tetracycline base, oxytetracycline HCl, and tetracycline HCl, were goitrogenic in rats fed a low iodine diet. This goitrogenic effect was accompanied by high radioactive iodine uptake. Administration of minocycline also produced a large goiter with high radioiodine uptake in rats fed a relatively high iodine diet.

Treatment of various animal species with this class of drugs has also resulted in the induction of thyroid hyperplasia in the following: in rats and dogs (minocycline); in chickens (chlortetracycline); and in rats and mice (oxytetracycline). Adrenal gland hyperplasia has been observed in goats and rats treated with oxytetracycline.

Results of animal studies indicate that tetracyclines cross the placenta and are found in fetal tissues.

15 REFERENCES

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3. Horne HW Jr. and Kundsin RB. The role of mycoplasma among 81 consecutive pregnancies: a prospective study. *Int J Fertil* 1980; 25: 315-317.
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7. Clinical and Laboratory Standards Institute (CLSI). *Performance Standards for Antimicrobial Disk Diffusion Susceptibility Tests; Approved Standard - Twelfth Edition.* CLSI document M02-A12, Clinical Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne Pennsylvania 19087, USA, 2015.
8. Clinical and Laboratory Standards Institute (CLSI). *Methods for Antimicrobial Dilution and Disk Susceptibility Testing of Infrequently Isolated or Fastidious Bacteria; Approved Guideline – Second Edition.* CLSI document M45-A2, Clinical Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne Pennsylvania 19087, USA, 2010.
9. Clinical and Laboratory Standards Institute (CLSI). *Methods for Antimicrobial Susceptibility Testing of Anaerobic Bacteria; Approved Standard – Eighth Edition*. CLSI document M11-A8, Clinical Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne Pennsylvania 19087, USA, 2012.
10. Clinical and Laboratory Standards Institute (CLSI). *Methods for Mycobacteria, Nocardiae, and Other Aerobic Actinomycetes; Approved Standard – Second Edition*. CLSI document M24-A2, Clinical Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne Pennsylvania 19087, USA, 2011.
11. Clinical and Laboratory Standards Institute (CLSI). *Methods for Antimicrobial Susceptibility Testing for Human Mycoplasmas; Approved Guideline*. CLSI document M43-A, Clinical Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne Pennsylvania 19087, USA, 2011.

16 HOW SUPPLIED/STORAGE AND HANDLING

Doryx MPC (doxycycline hyclate delayed-release tablets), 60 mg and 120 mg are white, oval tablets containing yellow pellets and debossed on one face with "D6" and "DC", respectively, and plain on the other. Each tablet contains doxycycline 60 mg or 120 mg (equivalent to doxycycline hyclate 69.4 mg or 138.8 mg).

The 60 mg tablet is supplied in bottles of 120 tablets NDC 51862-560-12

The 120 mg tablet is supplied in bottles of 60 tablets. NDC 51862-559-60

Store at 25° C (77° F); excursions permitted to 15°C to 30° C (59°F to 86° F) [see USP Controlled Room Temperature]. Dispense in a tight, light-resistant container (USP).

17 PATIENT COUNSELING INFORMATION

Advise patients taking Doryx MPC for malaria prophylaxis:

- that no present-day antimalarial agent, including doxycycline, guarantees protection against malaria.
- to avoid being bitten by mosquitoes by using personal protective measures that help avoid contact with mosquitoes, especially from dusk to dawn (for example, staying in well-screened areas, using mosquito nets, covering the body with clothing, and using an effective insect repellent).
- that doxycycline prophylaxis:
  - should begin 1 to 2 days before travel to the malarious area,
  - should be continued daily while in the malarious area and after leaving the malarious area,
  - should be continued for 4 further weeks to avoid development of malaria after returning from an endemic area,
  - should not exceed 4 months.

Advise all patients taking Doryx MPC:

- to avoid excessive sunlight or artificial ultraviolet light while receiving doxycycline and to discontinue therapy if phototoxicity (for example, skin eruptions, etc.) occurs. Sunscreen or sunblock should be considered [*see Warnings and Precautions (5.3)*]
- to drink fluids liberally along with Doryx MPC to reduce the risk of esophageal irritation and ulceration [*see Adverse Reactions (6.1)*]
- that the absorption of tetracyclines is reduced when taken with foods, especially those that contain calcium. [*see Drug Interactions (7.3)*]
- that the absorption of tetracyclines is reduced when taken with antacids containing aluminum, calcium or magnesium, bismuth subsalicylate, and iron-containing preparations [*see Drug Interactions (7.3)*].
- that the use of doxycycline might increase the incidence of vaginal candidiasis.

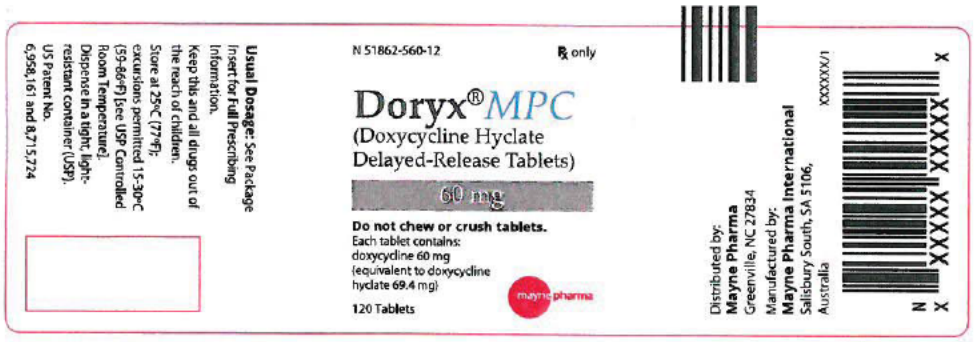
Advise patients that diarrhea is a common problem caused by antibacterial drugs which usually ends when the antibacterial is discontinued. Sometimes after starting treatment with antibacterial drugs, patients can develop watery and bloody stools (with or without stomach cramps and fever) even as late as two or more months after having taken the last dose of antibacterial. If this occurs, patients should contact their physician as soon as possible.

Counsel patients that antibacterial drugs including Doryx MPC should only be used to treat bacterial infections. They do not treat viral infections (for example, the common cold). When Doryx MPC is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by Doryx MPC or other antibacterial drugs in the future.

Manufactured by:
Mayne Pharma International Pty Ltd
1538 Main North Road
Salisbury South, SA 5106 Australia

Distributed by:
Mayne Pharma USA
Greenville, NC 27834
1-844-825-8500

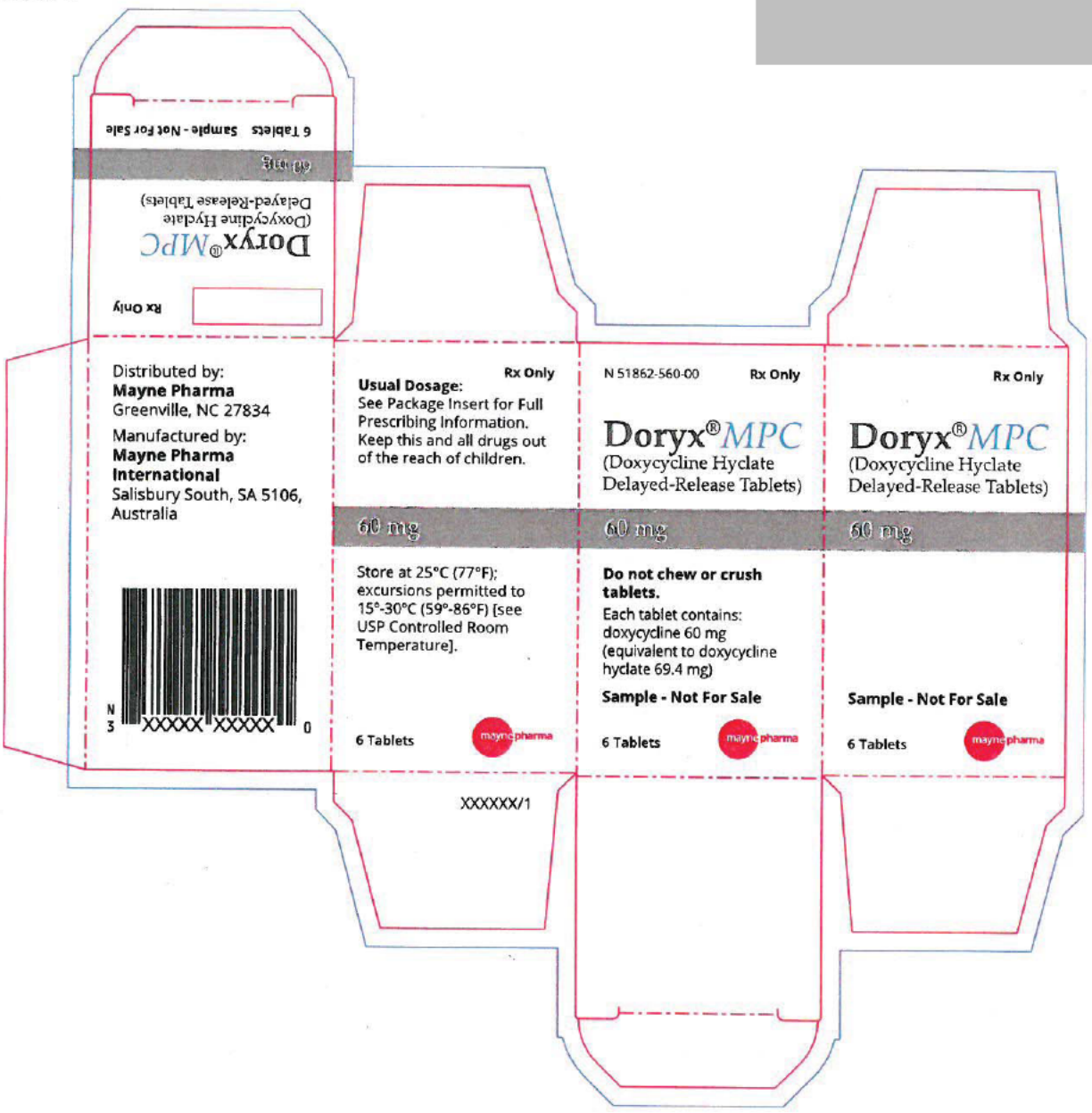
(b)(4)


45 mm
Usual Dosage: See Package Insert for Full Prescribing Information.
Keep this and all drugs out of the reach of children.
Store at 25°C (77°F); excursions permitted 15-30°C (59-86°F) [see USP Controlled Room Temperature].
Dispense in a tight, light-resistant container (USP).
US Patent No. 6,958,161 and 8,715,724
N 51862-560-12
℞ only
Doryx® MPC
(Doxycycline Hyclate Delayed-Release Tablets)
60 mg
Do not chew or crush tablets.
Each tablet contains:
doxycycline 60 mg
(equivalent to doxycycline hyclate 69.4 mg)
120 Tablets
mayne pharma
Distributed by:
Mayne Pharma
Greenville, NC 27834
Manufactured by:
Mayne Pharma International
Salisbury South, SA 5106,
Australia
XXXXX/1
N XXXXX XXXXX X
140 mm

(b)(4)

Option 1

(b)(4)



(b)(4)

Option 1

(b)(4)

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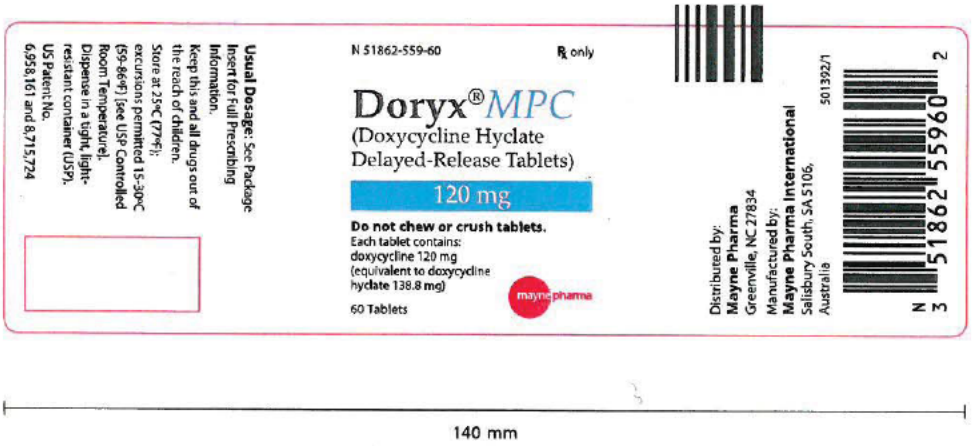
45 mm
Usual Dosage: See Package Insert for Full Prescribing Information.
Keep this and all drugs out of the reach of children.
Store at 25°C (77°F); excursions permitted 15-30°C (59-86°F) [see USP Controlled Room Temperature].
Dispense in a tight, light-resistant container (USP).
US Patent No. 6,958,161 and 8,715,724
N 51862-559-60
℞ only
Doryx®MPC
(Doxycycline Hyclate Delayed-Release Tablets)
120 mg
Do not chew or crush tablets.
Each tablet contains:
doxycycline 120 mg
(equivalent to doxycycline hyclate 138.8 mg)
60 Tablets
mayne pharma
Distributed by:
Mayne Pharma
Greenville, NC 27834
Manufactured by:
Mayne Pharma International
Salisbury South, SA 5106,
Australia
5013927
N 3 51862 55960 2
140 mm

(b)(4)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 50-795/ S-22

SUMMARY REVIEW

Division Director Decisional Memo

Date	(electronic stamp)
From	Sumathi Nambiar MD MPH
Subject	Division Director Decisional Memo
NDA #	50795/S-022
Applicant Name	Mayne Pharma International Pty Ltd
Date of Submission	July 20, 2015
PDUFA Goal Date	May 20, 2016
Established (USAN) Name	Doxycycline hyclate
Dosage Forms / Strength	60 mg and 120 mg tablets
Proposed Indications	All approved indications for Doryx
Recommended Action:	Approval

Material Reviewed/Consulted Action Package including:	**Names of Discipline Reviewers**
Product Quality Reviewer	Yonge Lu PhD
Cross-Discipline Team Leader Review	Elsbeth Chikhale PhD
Medical Officer Review	Edward Weinstein MD PhD
Clinical Microbiology Review	Simone Shurland PhD
Clinical Pharmacology Review	Dakshina Chilukuri PhD
Division of Medication Error Prevention and Analysis	Jacqueline Sheppard Pharm D

1.0 Introduction

Doryx delayed release tablets are currently approved in the following strengths: 50 mg, 75 mg, 80 mg, 100 mg, 150 mg and 200 mg. In the current formulation, doxycycline hyclate pellets with a pH dependent polymer coating (b) (4). This delays the release of doxycycline hyclate until the pellets reach the higher pH in the small intestine.

In this supplemental NDA (sNDA), the Applicant is proposing to add two new strengths (60 mg and 120 mg) with a modified (more acid resistant) formulation. The proposed 60 mg and 120 mg tablets with the modified formulation will not replace the current 50 mg and 100 mg Doryx tablets. The new strengths will be added to NDA 50795 under the trade name of Doryx MPC.

The Applicant submitted the results of a single-dose bioequivalence study comparing the proposed 120 mg tablets and the approved 100 mg Doryx tablets and requested a biowaiver for the proposed 60 mg tablets which is believed to be bioequivalent to the 50 mg Doryx tablets.

For a detailed discussion of this sNDA, please refer to the discipline specific reviews and the Cross-Discipline Team Leader Review. Only reviews specific to the issues in this sNDA will be discussed in this review.

2.0 Product Quality

No changes were proposed to the doxycycline hyclate drug substance. The proposed drug product is a tablet containing doxycycline pellets (b)(4) (b)(4) (b)(4) Apart from the formulation modification and the change in the dissolution specifications, (b)(4) from that currently approved for Doryx tablets. The CMC reviewer notes that the stability data support the approved shelf life of 24 months. (b)(4) (b)(4) to the drug substance or drug product facilities, no facilities were inspected to support this sNDA.

The Biopharmaceutics reviewer for this sNDA is Banu Zolnik, PhD. The proposed 120 mg tablets exhibit lower drug release in the acid stage (b)(4) drug released in 60 minutes) compared to the approved 100 mg tablets (b)(4) drug released in 60 minutes). Both formulations showed overlapping drug release profiles in the buffer stage.

The Applicant has requested a full waiver of the requirement for conducting bioequivalence studies for the Doryx MPC 60 mg tablets. The Applicant provided comparative dissolution data for the 60 mg and 120 mg tablets in the approved dissolution method as well in media with different pH values. Dr. Zolnik concludes that the Applicant has provided adequate comparative dissolution data to support the biowaiver request for the 60 mg strength Doryx MPC tablets and the biowaiver for this strength was granted.

The Applicant's proposed dissolution acceptance criteria for the proposed 60 mg and 120 mg Doryx MPC tablets (not more than (b) (4) in 60 minutes in the acid stage and Q= (b) (4) in 20 minutes in the buffer stage) are acceptable.

The Biopharmaceutics and CMC reviewers recommend approval of this sNDA. I concur with their assessment.

3.0 Clinical Pharmacology

Dakshina Chilukuri, PhD, is the clinical pharmacology reviewer for this sNDA. The Applicant has provided the results of Study 11450707, a single-dose bioequivalence study comparing Doryx MPC 120 mg tablet with Doryx 100 mg tablet in healthy adult subjects under fasted conditions. For the natural log-transformed data, the 90% confidence intervals for the geometric mean test-to-reference ratios for AUC_t, AUC_∞, and C_{max}, fell within the standard bioequivalence range of 80-125%. Therefore, Doryx MPC 120 mg was demonstrated to be bioequivalent to Doryx 100 mg tablets.

In an addendum dated May 06, 2016, Dr. Chilukuri notes that the bioanalytical site (b) (4) was not inspected as part of this sNDA review. The Office of Study Integrity and Surveillance (OSIS) has indicated that this site has been previously inspected on several occasions and no issues were identified during these inspections. The most recent inspection was conducted in (b)(4) and was found to be acceptable. Thus, the bioanalytical and PK results of Study 11450707 were deemed acceptable.

Dr. Chilukuri notes that the clinical pharmacology information provided by the Applicant is acceptable and supports approval of the sNDA pending review of the biowaiver request and agreement on labeling.

4.0 Clinical Microbiology

Simone Shurland, PhD, is the microbiology reviewer for this sNDA. No new microbiology data were submitted. Labeling recommendations provided by Dr. Shurland have been incorporated in labeling.

5.0 Clinical Efficacy/Safety

Edward Weinstein, MD PhD, is the clinical reviewer for this sNDA. No new clinical data were submitted in this sNDA. Dr. Weinstein notes that for children less than 45 kgs who require weight-based dosing, there is a potential for medication errors as the Doryx MPC 60 mg tablets are bioequivalent to the Doryx 50 mg tablets and the 120 mg Doryx MPC tablets are bioequivalent to the Doryx 100 mg tablets. This concern has been adequately addressed in labeling. (b)(5)

Dr. Weinstein recommends approval of this sNDA.

6.0 Labeling

Jacqueline Sheppard, PharmD, from DMEPA provided labeling revisions to the package insert, container, and carton. These revisions have been incorporated in labeling. Dr. Sheppard also notes that the proprietary name, Doxycycline MPC is acceptable.

7.0 Pediatrics

Under the Pediatric Research and Equity Act (PREA), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless the requirement is waived, deferred or inapplicable. As none of these criteria are applicable, this sNDA is exempt from PREA requirements.

8.0 Recommended Regulatory Action

I agree with the recommendations made by the review team and the cross-discipline team leader that NDA 50795/S-022 be approved.

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

/s/

SUMATHI NAMBIAR
05/20/2016

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 50-795/ S-22

OFFICER/EMPLOYEE LIST

Officer/Employee List

Application NDA 50-795/S-022 Doryx MPC (doxycycline hyclate delayed-release) 60 mg and 120 mg Tablets

The following list contains the names of all reviewers who wish to have their names included for those who have written, co-written and/or signed off on reviews and decision memos for this supplemental application.

Simone Shurland
Elsbeth Chikhale
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Lubna Merchant
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Kalavati Suvarna
Edward Weinstein

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 50-795/S-22

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	May 13, 2016
From	Elsbeth Chikhale, Ph.D. Biopharmaceutics Lead (Acting), Division of Biopharmaceutics, ONDP, OPQ
Subject	Cross-Discipline Team Leader Review
NDA	NDA 50795/ES-022
Type of Submission	Efficacy Supplement (proposing the addition of two new drug product strengths of 60 mg and 120 mg with a modified formulation and associated new name and labeling changes)
Applicant	Mayne Pharma International Pty Ltd.
Date of Submission	July 20, 2015
PDUFA Goal Date	May 20, 2016
Proprietary Name / Established (USAN) names	Doryx/ Doxycycline Hyclate Tablets, USP
Dosage forms / Strength	Delayed Release Oral Tablets/ 50 mg, 75 mg, 80 mg, 100 mg, 150 mg, and 200 mg
Proposed Indication(s)	Doxycycline hyclate is a tetracycline-class antibacterial indicated for: • Rickettsial infections • Sexually transmitted infections • Respiratory tract infections • Specific bacterial infections • Ophthalmic infections • Anthrax, including inhalational anthrax (post-exposure) • Alternative treatment for selected infections when penicillin is contraindicated • Adjunctive therapy in acute intestinal amebiasis and severe acne • Prophylaxis of malaria
Recommendation:	**APPROVAL** is recommended with labeling changes

This secondary CDTL review is based, on the primary reviews/memos of:

DICIPLINE	PRIMARY REVIEWER	FINAL REVIEW DATE
Pharmacology/Toxicology	N/A	
Chemistry/Manufacturing/ Controls	Yong De Lu, Ph.D.	5/6/2016
Quality Microbiology	N/A	
Quality Statistics (Biometrics)	N/A	
Biopharmaceutics	Banu Sizanli Zolnik, Ph.D.	4/19/2016
Clinical Pharmacology	Dakshina Chilukuri, Ph.D.	3/10/2016
Clinical	N/A	
Clinical Microbiology	N/A	
Clinical Statistics	N/A.	
Medication Error Prevention and Analysis	Jacqueline Sheppard, PharmD.	10/13/2015 (proprietary name) 10/13/2015 (labels & labeling)
Medication Error Prevention and Analysis	Deborah Myers, R.Ph., MBA	3/14/2016 (proprietary name) 4/28/2016 (labels & labeling)
Regulatory Project Manager	Carmen DeBellas, PharmD., R.Ph.	5/10/2016

Cross Discipline Team Leader Review

1. Introduction

Doryx (doxycycline hyclate delayed-release) tablets contain a tetracycline class antibacterial indicated for: Rickettsial infections, sexually transmitted infections, respiratory tract infections, specific bacterial infections, ophthalmic infections, anthrax, including inhalation anthrax (post-exposure), alternative treatment for selected infections when penicillin is contraindicated, adjunctive therapy in acute intestinal amebiasis and severe acne, and prophylaxis of malaria. Doryx is currently approved as 50 mg, 75 mg, 80 mg, 100 mg, 150 mg and 200 mg strength delayed release tablets. The currently approved Doryx tablet formulation described in NDA 50795 is a delayed release formulation of doxycycline hyclate, where doxycycline hyclate pellets are coated with a pH dependent polymer coating (b) (4) The currently approved Doryx tablets were designed to delay the release of doxycycline hyclate until the pellets reach the higher pH environment of the small intestine. Although the approved delayed release tablets are formulated using an acid resistant coating, in vitro dissolution results show that the approved Doryx tablets release a substantial amount of drug in acidic conditions ((b) (4) of the drug is released in vitro after 60 minutes in 0.06 N HCl). Because of the association between drug release in acid and the potential esophageal and gastric irritation, the Applicant stated that they have developed an alternative modified delayed release formulation with improved acid resistance.

2. Background

The drug substance doxycycline is a broad-spectrum antibiotic synthetically derived from oxytetracycline, and is available as doxycycline hyclate (doxycycline hydrochloride hemiethanolate hemihydrate) capsules and tablets for oral administration.

Doxycycline is a tetracycline-class antibacterial drug and is generally considered bacteriostatic. Tetracycline-class antibacterials inhibit protein synthesis in bacteria by binding to the 30S ribosomal subunit and blocking entry of amino-acyl tRNA molecules into the A site of the ribosome. This prevents incorporation of amino acid residues into elongating peptide chains. The antibacterial spectrum of doxycycline includes Gram-positive and Gram-negative organisms (including aerobic and anaerobic species), including methicillin-resistant *Staphylococcus aureus* (MRSA), and some Mycobacteria. Cross-resistance of these organisms to tetracycline is common.

Doxycycline is almost completely absorbed following oral administration. Tetracyclines as a class have varying degrees of protein binding. Doxycylcine is excreted in both the urine and the feces. Excretion of doxycycline by the kidney is about 40% in 72 hours in individuals with a creatinine clearance of about 75 mL/min. The half-life of doxycycline is 18-22 hours. Hemodialysis does not alter the serum half-life of doxycycline.

In this Efficacy Supplement 22 to the original NDA 50795, the Applicant is proposing to add two new strengths (60 mg and 120 mg) with a modified (more acid resistant) formulation. The Applicant claims that the newly proposed 120 mg tablet is BE to the currently approved 100 mg tablet. The Applicant submitted a single dose bioequivalence study comparing the proposed 120 mg strength tablets and the approved 100 mg Doryx tablets. The Applicant has requested a biowaiver for the newly proposed 60 mg strength tablets which is believed to be BE to the 50 mg Doryx tablets. The Applicant stated that the proposed 60 mg and 120 mg tablets with the modified formulation will not replace the current 50 mg and 100 mg Doryx tablets; rather the new strengths will be added to NDA 50795 as an alternative under the Doryx MPC trade name. It is emphasized in the submission that the currently approved Doryx tablets will remain unchanged and will be continued to be marketed. To avoid confusion a modifier to the Doryx name (b)(4), which was not acceptable and Doryx MPC, which was found acceptable) and labeling changes with new dosing instructions are proposed.

Per FDA Guidance for Industry SUPAC-MR: Modified Release Solid Oral Dosage Forms, the proposed formulation change for Doryx MPC is classified as a Level 3 change in formulation compared to the approved formulation, involving the "Addition or deletion of release controlling excipients (e.g., release controlling polymers/plasticizers)". Accordingly, the following documentation is included in this submission:

- Updated product release specifications and executed batch records for 3 batches of each strength of Doryx MPC (60 mg and 120 mg).
- Six months long term and accelerated stability data for three batches of each strength of Doryx MPC (60 mg and 120 mg) with a commitment to submit long-term stability data for the first 3 production batches of each strength in future annual reports.
- Comparative dissolution profiles for Doryx MPC tablets and the currently approved Doryx tablets indicating the increased (in vitro) acid resistance of the modified formulation.
- A single-dose bioequivalence study comparing 1 x Doryx MPC 120 mg tablet (modified formulation) with 1 x Doryx 100 mg tablet (currently approved formulation).
- A biowaiver request for the Doryx MPC 60 mg tablet (modified formulation).

3. Quality CMC

- **General Quality Considerations**

Drug Substance: The Applicant did not propose any changes to the doxycycline hyclate drug substance.

Drug Product:
The proposed modified formulation, Doryx MPC (previously called (b)(4) designated with the product code MP336, is a tablet containing yellow delayed release doxycycline hyclate pellets (MP336 Pellets) presented in (b)(4) 60 mg and 120 mg strengths. The pellets (b)(4) (b)(4). The same

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Updated product release specifications and executed batch records for three batches of each strength of Doryx MPC were provided. All testing results meet the approved release specifications.

- **Stability:**

For the stability program, (b)(4) were manufactured (b)(4) (b)(4) 60 mg and 120 mg Doryx MPC tablets. The tablets were packaged into their various container closure systems and representative batches were placed in the stability program.

The CMC review concludes that the NDA provided sufficient stability information on the drug product to assure identity, strength, purity, and quality of the drug product through the approved shelf life of 24 months.

- **Facilities Review/Inspection:**

The Applicant did not propose any changes to the drug substance or drug product facilities. Therefore, no facilities were inspected to support this efficacy supplement (ES-022).

- **Quality Overall Recommendation:**

Based on the CMC information provided in this submission and the Biopharmaceutics review recommending approval, from the product quality perspective the application is satisfactory to assure the identity, strength, purity and quality of the drug product.

From the CMC perspective this supplement is recommended for approval. For full details refer to the CMC review by Dr. Yong De Lu dated May 6, 2016.

4. Quality Microbiology

N/A. The Applicant did not propose any changes to the microbiological testing conducted to assure the quality of the newly proposed tablets. Therefore, no Quality Microbiologist was assigned.

5. Quality Statistics

N/A.

6. Nonclinical Pharmacology/Toxicology

N/A. No new pharmacology/ toxicology data were submitted to support this efficacy supplement.

7. Biopharmaceutics

The Biopharmaceutics review focuses on the evaluation of 1) multi-point dissolution profiles using the approved dissolution method to support of the approval of the proposed 120 mg Doryx MPC tablets, 2) the biowaiver request for 60 mg Doryx MPC tablets, and 3) the proposed dissolution acceptance criteria for the proposed 60 mg and 120 mg Doryx MPC tablets.

Dissolution data supporting the approval of the 120 mg strength tablets

The Applicant provided comparative dissolution data between the proposed 120 mg and the approved 100 mg strengths Doryx tablets using the approved dissolution method (0.06N HCL stage and pH 5.5 buffer stage) as well as in pH 1.2, pH 4.5 and pH 6.8 media. The newly proposed 120 mg Doryx MPC tablets exhibit a lower drug release in the acid stage (b) (4) drug released in 60 minutes for the proposed 120 mg strength vs. (b) (4) drug released in 60 minutes for the approved 100 mg strength tablets). Both formulations exhibited overlapping drug release profiles in the buffer stage. Both formulations showed differences in drug release in pH 1.2 and pH 4.5 buffers, while drug release was similar in pH 6.8 buffer. Therefore, the provided comparative dissolution data support the claim that the modified formulation has a lower drug release rate in acid (is more acid resistant in vitro) than the currently approved formulation.

The dissolution data supporting the request to waive the requirement for conducting a bioequivalence study for the 60 mg strength Doryx MPC tablets

The Applicant has requested a full waiver of the requirement for conducting bioequivalence studies for the Doryx MPC Tablet 60 mg. The approval of the 60 mg strength Doryx MPC tablet is based on the following:

a) An acceptable bioequivalence study comparing the proposed 120 mg Doryx MPC to the approved 100 mg Doryx tablet
b) Similarity between the dissolution profiles of the proposed 60 mg Doryx MPC tablets and the proposed 120 mg Doryx MPC tablets.
c) The proposed 60 mg Doryx MPC tablet is (b)(4) to the 120 mg Doryx MPC tablet. Both strengths are manufactured (b)(4) (b) (4) (b)(4) the strengths is the (b) (4)

The Applicant provided comparative dissolution data between the 60 mg and 120 mg strength tasblets in the approved dissolution method (0.06N HCL and pH 5.5 buffer stages) as well as pH 1.2, pH 4.5 and pH 6.8 media. Drug release profiles are similar between the proposed 60 mg and 120 mg strength Doryx MPC tablets in the approved dissolution method-acid and buffer stage as well as pH 1.2, 4.5 and 6.8 buffers. Therefore, the provided comparative dissolution data supports the biowaiver request for the 60 mg strength Doryx MPC tablets and the biowaiver for this strength was granted.

Evaluation for the proposed dissolution acceptance criterion in the acid stage

The Applicant proposes a dissolution acceptance criterion of no more than (b) (4) at 60 minutes for Doryx MPC, 60 mg and 120 mg, in the acid stage. This is different than the approved dissolution acceptance criterion for Doryx tablets (50, 75, 80, 100, 150, and 200 mg) in acid

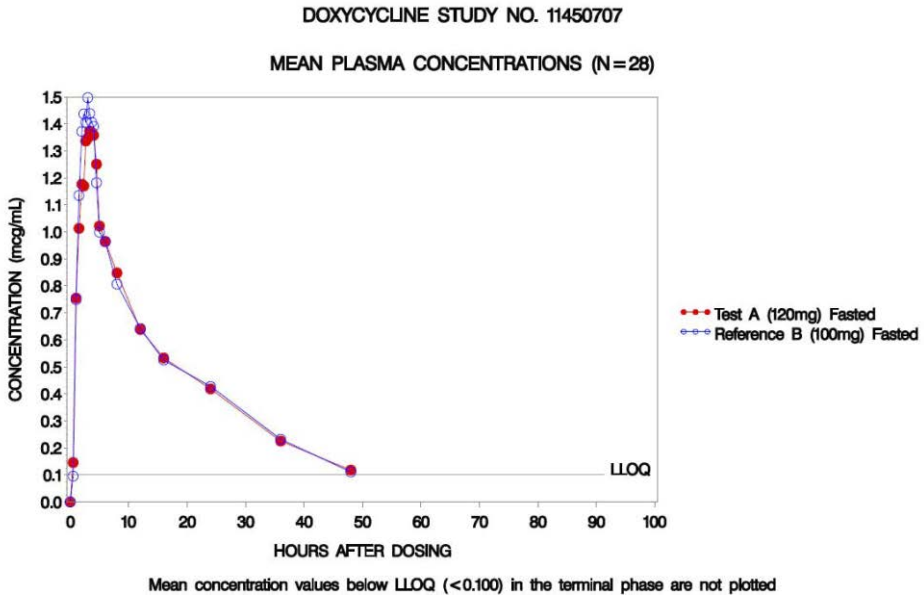
media, which is not more than (b) (4) at 20 minutes. The Applicant is proposing a dissolution acceptance criterion in the buffer stage of Q= (b) (4) at 20 minutes for the newly proposed 60 mg and 120 mg Doryx MPC tablets, which is the same as the buffer stage dissolution acceptance criterion approved for the 50, 75, 80, 100, 150, and 200 mg Doryx tablets. The Applicant's proposed dissolution acceptance criteria for the newly proposed 60 mg and 120 mg Doryx MPC tablets (not more than (b) (4) in 60 minutes in the acid stage and Q= (b) (4) in 20 minutes in the buffer stage) are acceptable based on the provided dissolution data**.**

The Biopharmaceutics Reviewer is recommending APPROVAL of this NDA supplement for Doryx MPC, 60 mg and 120 mg tablets. For full details refer to the Biopharmaceutics review by Dr. Banu Sizanli Zolnik dated 4/19/16.

8. Clinical Pharmacology

The approval of the proposed 120 mg strength Doryx MPC is based on the bioequivalence study (#11450707) comparing the proposed 120 mg strength Doryx MPC tablets to the approved 100 mg Doryx tablets. The Office of Clinical Pharmacology (refer to the Clinical Pharmacology review dated 3/10/2016 by Dr. Dakshina Chilukuri) reviewed Study 11450707, which is a single-dose bioequivalence study comparing 1 x Doryx MPC120 mg tablet (modified formulation drug product) with 1 x Doryx 100 mg tablet (currently approved drug product) in healthy adult subjects under fasted conditions. For the natural log-transformed data for doxycycline, the 90% confidence intervals on the geometric mean test-to-reference ratios for AUC_t, AUC_∞, and C_{max}, fell within the standard bioequivalence range of 80.00-125.00%. Therefore, the test formulation of doxycycline hyclate 120 mg DR Tablet (Doryx MPC manufactured by Mayne Pharma International Pty. Ltd.) was demonstrated to be bioequivalent to the reference formulation, doxycycline hyclate delayed-release tablets (100 mg Doryx tablets). The mean plasma concentration-time profiles are illustrated in the next Figure.

Figure 1. Mean Concentration versus Time Plot (Linear): Doxycycline



The 90% confidence intervals for C_{max}, AUC_{0-t}, and AUC_{0-inf} are presented in the Table below.

Table 2.1 Summary of Study Results Based on Plasma Doxycycline Concentrations

Study No.: 11450707

Plasma PK and BE Parameters of Doxycycline

Parameter	Trt	# Datasets	LS Geometric Mean	Contrast (# subjects)	LSGM Ratio (%)	90% Confidence Interval (%)	ISCV(%)	P-value Period	P-value Sequence	BE Outcome
AUC 0-t (mcg·hr/mL)	A	28	22.09	A vs B (n=28)	100.67	91.66-110.56	20.8	0.6584	0.7953	Pass
	B	28	21.94							
AUC 0-∞ (mcg·hr/mL)	A	28	25.60	A vs B (n=28)	100.43	92.18-109.42	19.0	0.4716	0.9227	Pass
	B	28	25.49							
C_{max} (mcg/mL)	A	28	1.512	A vs B (n=28)	98.68	89.38-108.95	22.0	0.6367	0.9624	Pass
	B	28	1.532							

Although Doryx MPC Tablets contain 20% more administered drug but achieves a comparable rate and extent of exposure as Doryx Tablets, the benefit/risk assessment of Doryx MPC remains favorable given the reduced potential for gastric irritation. In addition, the proposed dosing instructions for the Doryx MPC Tablets are well within the approved dosing window of the Doryx Tablet, which includes a 200 mg dose strength. There were no serious adverse events reported during the BE study.

The Clinical Pharmacology review concludes that the BE study conducted by the Applicant indicates that the test formulation of Doxycycline Hyclate Delayed-Release Tablets, 120 mg meets the 90% CI criterion for log transformed AUC_{0-t}, AUC_{0-inf}, and C_{max} and, therefore, has shown equivalent bioavailability to a similar dosage of the reference formulation, Doxycycline Hyclate Delayed-Release Tablets USP, 100 mg. The Clinical Pharmacology review recommends APPROVAL of this supplement (S-022) to NDA 50795. For full details refer to the Clinical Pharmacology review by Dr. Dakshina Chilukuri dated 3/10/2016.

9. Clinical

N/A. There were no clinical studies conducted for the purpose of evaluating efficacy and safety. The Applicant is relying on the BE study discussed under the Clinical Pharmacology section of this CDTL review and FDA's previous findings of safety and effectiveness for the approved drug product.

10. Clinical Microbiology

N/A. No new Microbiology studies were submitted in the NDA supplement. This proposed doxycycline new strengths fall within the approved strengths and the same indications will be used as the approved product.

11. Clinical Statistical

N/A. There were no clinical studies conducted for the purpose of evaluating efficacy and safety. Therefore, there is no Clinical Statistics review for this supplement.

12. Safety

N/A. There were no clinical studies conducted for the purpose of evaluating efficacy and safety. There were no serious adverse events reported during the BE study.

13. Advisory Committee Meeting

The current submission did not go to an Advisory Committee Meeting.

14. Pediatrics

Doxycycline hyclate commercial products are currently approved for pediatric patients >8 years of age.

15. Other Relevant Regulatory Issues

There are no other relevant regulatory issues with this application.

16. Labeling:

- **Proprietary Name:** In the original supplement (S-022), the name (b) (4) was proposed for the newly proposed 60 mg and 120 mg tablets with a modified formulation; however this name was not accepted by the Division of Medication Error Prevention and Analysis (DMEPA) (see DMEPA Review by Jacqueline Sheppard, Pharm.D. dated 10/13/2015). Therefore, the Applicant proposed a new name “Doryx MPC” (MPC stands for Modified Polymer Coat), in an

amendment to this supplement dated 12/24/2015. The Applicant's newly proposed proprietary name "Doryx MPC" has been reviewed by DMEPA and found acceptable from both promotional and safety perspectives. For details refer to the DMEPA review by Deborah Myers, R.Ph., MBA dated 3/14/2016.

- DMEPA also evaluated the Product Information/Prescribing Information, FDA Adverse Event Reporting System (FAERS), Previous DMEPA Reviews, ISMP Newsletters, and Proposed Labels and Labeling. The review by Jacqueline Sheppard Pharm.D. concludes that the submitted labels and labeling may be improved and recommends several revisions. For full details refer to the DMEPA review by Jacqueline Sheppard Pharm.D. dated 10/13/2015. The Applicant submitted revised container and carton labels on 12/23/2015. The revisions to the container and carton labels were found acceptable from a medication error perspective; however, DMEPA identified additional areas of the label and labeling that can be revised to increase clarity, improve readability, and add important information to mitigate medication errors and promote the safe use of Doryx MPC. For full details refer to the DMEPA review by Deborah Myers, R.Ph., MBA dated 4/28/2016.

- **Labeling Revisions:** Several revisions were recommended for the proposed labeling by CMC and DMEPA. For the specific recommendations refer to the individual reviews from these disciplines. In addition, an information request was sent to the Applicant on 5/9/2016 with the following recommendation for the equivalency statement on the carton and container labels:

  For DORYX MPC Tablets 60 mg:
  Each tablet contains: doxycycline 60 mg (equivalent to doxycycline hyclate 69.4 mg)

  For DORYX MPC Tablets 120 mg:
  Each tablet contains: doxycycline 120 mg (equivalent to doxycycline hyclate 138.8 mg)

- The Regulatory Project Manager conducted a review of the Physician Labeling Rule (PLR) format of the prescribing information (PI). The review concluded that no Selected Requirement of Prescribing Information (SRPI) format deficiencies were identified. For full details refer to the PLR format review by Carmen DeBellas, Pharm.D., R.Ph. dated 5/10/2016.

- It is noted that there were no labeling meetings held for this efficacy supplement. Table 1 below shows the difference in the dosing between Doryx and Doryx MPC.

Table 1. Relevant Product Information for Doryx MPC and Doryx		
Product Name	**Doryx MPC**	**Doryx**
Initial Approval Date	N/A	July 21, 2004 (tablet)
Active Ingredient	Doxycycline Hyclate	Doxycyline Hyclate
Proposed Pronunciation	dor -x M P C	dor -x
Indication	Treatment or prophylaxis of the following conditions or diseases: rickettsial infections, sexually transmitted infections, respiratory tract infections, specific bacterial infections, ophthalmic infections, anthrax, alternative treatment for selected infections when penicillin is contraindicated, adjunctive therapy for acute intestinal amebiasis and severe acne, and prophylaxis of malaria.	
Route of Administration	Oral	Oral
Dosage Form	Delayed-release Tablet	Delayed-release Tablet
Strengths	60 mg and 120 mg	50 mg, 75 mg, 80 mg, 100 mg, 150 mg, and 200 mg
Dose and Frequency	Adults: 240 mg on the first day of treatment (administered 120 mg every 12 hours) followed by a maintenance dose of 120 mg daily. The maintenance dose may be administered as a single dose or as 60 mg every 12 hours. In the management of more severe infections (particularly chronic infections of the urinary tract), 120 mg every 12 hours is recommended. Pediatric: The recommended dosage schedule for children weighing 45 kg or less is 5.3 mg/kg of body weight divided into two doses on the first day of treatment, followed by 2.6 mg/kg of body weight given as a single daily dose or divided into two doses on subsequent days. For more severe infections up to (b) (4) mg/kg of body weight may be used. For children over 45 kg, the usual adult dose should be used.	Adults: 200 mg on the first day of treatment (administered 100 mg every 12 hours) followed by a maintenance dose of 100 mg daily. The maintenance dose may be administered as a single dose or as 50 mg every 12 hours. In the management of more severe infections (particularly chronic infections of the urinary tract), 100 mg every 12 hours is recommended. Pediatric: The recommended dosage schedule for children weighing 45 kg or less is 4.4 mg/kg of body weight divided into two doses on the first day of treatment, followed by 2.2 mg/kg of body weight given as a single daily dose or divided into two doses on subsequent days. For more severe infections up to 4.4 mg/kg of body weight may be used. For children over 45 kg, the usual adult dose should be used.
How Supplied	60 and 120 count bottles	60 and 120 count bottles
Storage	Controlled Room Temperature	Controlled Room Temperature

- **Labeling conclusion:** At the time of this review, a draft proposal for labeling changes that include the overall DAIP's recommendations should be conveyed to the Applicant. A final agreement with the Applicant should be reached on the recommended labeling changes before a regulatory action is taken for this NDA supplement.

17. Recommendations/Risk Benefit Assessment

- ***Recommended Regulatory Action:*** **APROVAL** with labeling changes is recommended for NDA 50795/S-022 for Doryx MPC (Doxycycline Hyclate) Delayed Release Tablets, 60 mg and 120 mg.

- ***Risk Benefit Assessment:*** The 60 mg and 120 mg tablets Doryx MPC tablets with a modified formulation are designed to have an improved acid resistance, thereby, in theory, potentially reducing the esophageal and gastric irritation associated with Doryx. There were no clinical studies submitted to show this potential benefit. Although Doryx MPC Tablets contain 20% more administered drug but achieves a comparable rate and extent of exposure as Doryx Tablets, the benefit/risk assessment of Doryx MPC remains favorable given the reduced potential for gastric irritation. In addition, the proposed dosing instructions for the Doryx MPC Tablets are well within the approved dosing window of the Doryx Tablet, which includes a 200 mg dose strength. The doxycycline label informs providers on risks and benefits associated with doxycycline use. No additional safety concerns are expected to be associated with the proposed 60 mg and 120 mg Doryx MPC tablets.

- ***Recommendation for Postmarketing Risk Evaluation and Management Strategies***: Based on the information available in the current submission and the understanding of Doxycycline Hyclate approved therapy, there are no specific recommendations for post-market risk evaluation and mitigation strategies.

- ***Recommended Comments to Applicant:*** No comments need to be conveyed to the Applicant in the regulatory action letter. However, it is noted that the Applicant should be asked to revise the drug product's labeling as recommended by the Division.

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/s/

ELSBETH G CHIKHALE
05/13/2016

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 50-795/S-22

CLINICAL REVIEW

CLINICAL REVIEW

Application Type	NDA 505 (b)(2) Efficacy Supplement
Application Number	NDA 50-795/S-022
Priority or Standard	Standard
Submit Date	July 13, 2015
Received Date	July 20, 2015
PDUFA Goal Date	May 20, 2016
Division / Office	Division of Anti-Infective Products / Office of Antimicrobial Products
Reviewer Name	Edward Weinstein, MD, PhD
Review Completion Date	April 27, 2016
Established Name	Doxycycline Hyclate
(Proposed) Trade Name	Doryx MPC™
Therapeutic Class	Tetracycline-class antibacterial
Applicant	Mayne Pharma
Formulation	Delayed-Release Tablets, 60 mg and 120 mg
Dosing Regimen	Multiple
Indications	Multiple anti-infective indications
Intended Population	Adults and children > 8 years of age; (b)(4) (b)(4)

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

The reviewer recommends approval of this 505(b)(2) efficacy supplement for a modified formulation of doxycycline hyclate for the same indications as the currently approved Doryx® formulation.

1.2 Risk Benefit Assessment

Doxycycline is effective for the approved indications and remains a preferred treatment option against pathogens such as *Chlamydia*, *Rickettsia*, *Vibrio* and *Mycoplasma* species. The doxycycline label adequately informs providers on risks and benefits associated with doxycycline use.

This 505(b)(2) NDA efficacy supplement for polymer coated, delayed release doxycycline hyclate 60 mg and 120 mg tablets relies on FDA's previous findings of safety and effectiveness for the reference drug, Doryx (doxycycline hyclate) tablets approved on May 6, 2005. The new formulation has increased *in vitro* resistance to dissolution in acid, at the expense of decreased bioavailability. The Doryx MPC 60 mg tablets are bioequivalent to the Doryx 50 mg tablets, and the 120 mg Doryx MPC are bioequivalent to Doryx 100 mg tablets. This presents a concern for dosing errors for pediatric patients less than 45 kg who require weight based dosing. Specific dosage and administration labelling statements have been added to reduce the potential for confusion. No additional safety concerns are expected to be associated with the 60 mg and 120 mg tablets.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None

1.4 Recommendations for Postmarket Requirements and Commitments

None

2 Introduction and Regulatory Background

The currently approved Doryx tablet formulation in NDA 50-795 is a delayed-release formulation of doxycycline hyclate, where doxycycline hyclate pellets are coated with a pH dependent polymer coating (b) (4) The proposed drug product, Doryx MPC, is a new formulation of Doryx with further reduced tablet dissolution properties under acidic conditions. While not specifically tested in the studies within the submission, this formulation is believed by the Applicant to result in reduced doxycycline-associated gastric and esophageal irritation. The proposed formulation will provide an alternative product and not replace the current Doryx formulation in NDA 50-795.

The proposed 60 mg and 120 mg tablets would be equivalent to the currently approved Doryx 50 mg and 100 mg tablets, respectively. The 60 mg tablet would provide appropriate dosing for pediatric patients weighing (b)(4) to be dosed a (b)(4) (b)(4) of body weight once or twice daily. All other attributes, such as active ingredient, dosage form, route of administration, conditions of use, indications and dosing regimens are the same as Doryx. In support of this NDA, the applicant has submitted *in vitro* tablet dissolution profiles and a single pharmacokinetic study (Study 11450707) demonstrating bioequivalence of the 120 mg test formulation to the approved 100 mg formulation.

The supplement was originally submitted as a Prior Approval Supplement on July 13, 2015 and was subsequently deemed by the Division to be an efficacy supplement due to the presence of clinical data.

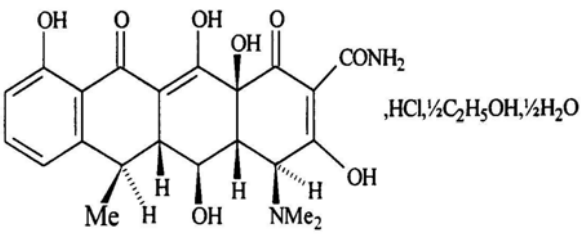
2.1 Product Information

Doxycycline is a tetracycline-class antibacterial drug and is generally considered bacteriostatic.

Tetracycline-class antibacterials inhibit protein synthesis in bacteria by binding to the 30S ribosomal subunit and blocking entry of amino-acyl tRNA molecules into the A site of the ribosome. This prevents incorporation of amino acid residues into elongating peptide chains.

Molecular structure of doxycycline is presented in Figure 1.

Figure 1: Molecular Structure of Doxycycline



The antibacterial spectrum of doxycycline includes Gram-positive and Gram-negative organisms (including aerobic and anaerobic species), including methicillin-resistant *Staphylococcus aureus* (MRSA), and some Mycobacteria. Cross-resistance of these organisms to tetracycline is common.

2.2 Tables of Currently Available Treatments for Proposed Indications

Not applicable.

2.3 Availability of Proposed Active Ingredient in the United States

A query of the Agency's Orange Book of approved doxycycline drug products with infectious disease indications yielded the products listed in Table 1.

Table 1: List of Approved Doxycycline Drug Product NDAs

Application Number	RLD	Active Ingredient	Dosage Form; Route	Strength	Proprietary Name	Applicant
N208253	N.D.	DOXYCYCLINE HYCLATE	CAPSULE; ORAL	EQ 75 MG BASE	ACTICLATE CAP	AQUA PHARMS LLC
N205931	Yes	DOXYCYCLINE HYCLATE	TABLET;ORAL	EQ 150MG BASE	ACTICLATE	AQUA PHARMS LLC
N205931	No	DOXYCYCLINE HYCLATE	TABLET;ORAL	EQ 75MG BASE	ACTICLATE	AQUA PHARMS LLC
N050805	Yes	DOXYCYCLINE	CAPSULE;ORAL	40MG	ORACEA	GALDERMA LABS LP
N050795	No	DOXYCYCLINE HYCLATE	TABLET, DELAYED RELEASE;ORAL	EQ 100MG BASE	DORYX	MAYNE PHARMA
N050795	No	DOXYCYCLINE HYCLATE	TABLET, DELAYED RELEASE;ORAL	EQ 150MG BASE	DORYX	MAYNE PHARMA
N050795	Yes	DOXYCYCLINE HYCLATE	TABLET, DELAYED RELEASE;ORAL	EQ 200MG BASE	DORYX	MAYNE PHARMA

N050795	No	DOXYCYCLINE HYCLATE	TABLET, DELAYED RELEASE;ORAL	EQ 75MG BASE	DORYX	MAYNE PHARMA
N050795	No	DOXYCYCLINE HYCLATE	TABLET, DELAYED RELEASE;ORAL	EQ 80MG BASE	DORYX	MAYNE PHARMA
N050795	No	DOXYCYCLINE HYCLATE	TABLET, DELAYED RELEASE;ORAL	EQ 50MG BASE	DOXTERIC	MAYNE PHARMA
N050751	Yes	DOXYCYCLINE HYCLATE	SYSTEM, EXTENDED RELEASE;PERIODONTAL	50MG	ATRIDOX	TOLMAR
N050641	Yes	DOXYCYCLINE	CAPSULE;ORAL	EQ 100MG BASE	MONODOX	AQUA PHARMS
N050641	No	DOXYCYCLINE	CAPSULE;ORAL	EQ 50MG BASE	MONODOX	AQUA PHARMS
N050641	No	DOXYCYCLINE	CAPSULE;ORAL	EQ 75MG BASE	MONODOX	AQUA PHARMS
N050480	Yes	DOXYCYCLINE CALCIUM	SUSPENSION;ORAL	EQ 50MG BASE/5ML	VIBRAMYCIN	PFIZER
N050007	Yes	DOXYCYCLINE HYCLATE	CAPSULE;ORAL	EQ 100MG BASE	VIBRAMYCIN	PFIZER
N050006	Yes	DOXYCYCLINE	FOR SUSPENSION;ORAL	EQ 25MG BASE/5ML	VIBRAMYCIN	PFIZER

N.D.: Not Determined

MO comment*: The proposed products in this application are 120 mg and 60 mg strength doxycycline hyclate tablets, bio-equivalent to100 mg and 50 mg strengths of other doxycycline hyclate products. Some doxycycline products have non-infectious disease indications, such as Oracea for the treatment of rosacea and Atridox for periodontal disease. Multiple doxycycline hyclate products have been discontinued, but none for reasons involving safety or efficacy.*

2.4 Important Safety Issues With Consideration to Related Drugs

Doxycycline has a safety profile that is similar to other tetracyclines whose major safety issues include permanent discoloration of the teeth and bone if administered during development, the development of *Clostridium difficile* associated diarrhea, photosensitivity, overgrowth of non-susceptible organisms, intracranial hypertension, and anti-anabolic activity.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Not applicable.

3 Ethics and Good Clinical Practices

This 505(b)(2) efficacy supplement and includes one bioequivalence/bioavailability study which does not raise any ethical concerns.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

The reader is referred to Doryx (Doxycycline Hyclate Delayed-release tablets) labeling for additional information on clinical pharmacology, clinical microbiology, pharmacodynamics and pharmacokinetics of doxycycline[1].

4.1 Chemistry Manufacturing and Controls

The reader is referred to the chemistry manufacturing and controls (CMC) review by Dr. Yong De Lu.

4.2 Clinical Microbiology

The reader is referred to the microbiology review by Dr. Simone Shurland for additional information.

4.3 Preclinical Pharmacology/Toxicology

No pharmacology/toxicology studies were included in this submission. The pharmacology/toxicology reviewer for this product is Dr. Amy Nostrandt.

4.4 Clinical Pharmacology

The reader is referred to the clinical pharmacology review by Dr. Dakshina Chilukuri for detailed analysis. In summary, a single-dose bioequivalence study (Study 11450707) comparing 1 x Doryx MPC™120 mg tablet (modified formulation drug product) with 1 x Doryx™ 100 mg tablet (currently approved drug product). Although the Orange Book identifies the Doryx™ 200 mg tablet as the Reference Listed Drug, the Doryx™ 100 mg tablet was used as the comparator in the submitted biostudy as: (i) the Doryx™ 100 mg strength tablet was expected to be bioequivalent to the Doryx MPC™120 mg tablet, and (ii) NDA 50-795 already contains biostudies demonstrating the bioequivalence of 2 x Doryx™ 100 mg tablets to 1 x Doryx™ 200 mg tablets. The study was a single-dose, randomized, 2-treatment, 2-way crossover study in healthy fasted volunteers and are summarized in Table 2. No other clinical pharmacology studies were conducted.

[1] http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/050795s018lbl.pdf

Table 2: Summary Clinical Bioequivalence Studies

Study No.	Study Objectives	Test Product(s) Dosing Regimen	Number of Subjects
11450707	Evaluate the relative Bioavailability of a new drug product compared to a marketed reference product	1 x 120 mg Doxycycline Hyclate Delayed-Release Tablet (14 Day interval between doses)	28 (28 included in statistical analysis)

The clinical pharmacology information provided by the Applicant was found to be acceptable and it was concluded that the proposed formulation met the bioequivalence criteria (the 90% confidence intervals on the geometric mean test-to-reference ratios for AUC and C_{max}, fell within the standard bioequivalence range of 80.00-125.00%).

5 Sources of Clinical Data

The Applicant is relying on (1) a bioavailability/bioequivalence studies conducted by (b) (4) (2) previous findings of safety and efficacy for the reference listed drug (RLD). The application did not utilize any published literature as a source of clinical data.

6 Review of Efficacy

Efficacy Summary

There were no clinical studies conducted for the purpose of evaluating efficacy. The Applicant is relying on previous findings of efficacy for the approved drug.

7 Review of Safety

Safety Summary

There were no clinical studies conducted for the purpose of evaluating safety. The Applicant is relying on previous findings of safety for the approved drug.

However, safety assessments of adverse events were made for the pharmacokinetic study conducted to demonstrate bioequivalence of Doryx MPC to Doryx. Case report forms were reviewed. There were no deaths or serious adverse events reported in the study.

7.1 Study 11450707

No serious adverse events were reported in the bioequivalence study.

In study 11450707, Mayne's Doryx MPC doxycycline hyclate tablet, 120 mg was compared to Doryx (doxycycline hyclate) 100 mg tablets in 28 healthy volunteers using a randomized, single-dose, two-treatment, two-period, crossover design under fasting conditions. All of the 28 study participants completed the study. A total of 16 adverse events (9 Doryx MPC product, 7 Doryx) were reported by 8 of the 28 subjects who participated in this study. All reported adverse events were considered "mild" by the investigator and spontaneously resolved by study completion. The most frequently reported adverse event for both the test and reference products were headache (Doryx MPC product: 1 subject; Reference Doryx product: 1 subject) and sore throat (Doryx MPC product: 1 subject; Reference Doryx product: 1 subject).

Physical and Laboratory Findings:
In the study, vital signs (blood pressure and heart rate) were measured prior to dosing and upon completion of the study drug. There were no clinically significant changes in the measured vital signs. Blood samples were collected at the time of the last pharmacokinetic blood sample collection of the study for post-study hematology and chemistry. All values were within 20% of the normal range.

MO comment: *The reported adverse events did not represent any significant new safety findings for doxycycline hyclate.*

7.2 Database Queries

A search of the Entrez PubMed database was conducted with the terms "doxycycline" and "adverse reaction" for the period from February 1, 2011 to present.

The Entrez PubMed search identified a case report and a comparative analysis of adverse drug reactions attributed to tetracycline class antibiotics in France between 1985 and 2007. The case report described a generalized bullous fixed drug eruption [1], and the analysis of tetracyclines did not identify any new or unexpected adverse reactions [2]. The fixed drug eruption is a known rare adverse reaction associated with tetracycline use [3]. The package insert for the RLD lists several skin adverse reactions that may have bullous manifestations, such as Stevens -Johnson syndrome and toxic epidermal necrolysis.

A case report by Moy and Kapila (2016)[4] describes probable doxycycline-induced pancreatitis in a 51-year-old man on empiric therapy for Lyme disease who required

intubation and admission to the intensive care unit. This report triggered a further search for "pancreatitis" and "doxycycline" within Entrez Pubmed. A report was identified from Wachira and colleagues (2013)[5] describing the case of a 21-year-old female with pancreatitis following doxycycline treatment for an upper respiratory infection. Several other reports of doxycycline associated acute pancreatitis have been published in the scientific literature[6-8]. Tetracycline and tigecycline, both tetracycline-class drugs, have been implicated as causes of acute pancreatitis[9-10]. Acute pancreatitis is listed as an adverse reaction in the Minocin® (minocycline) package insert and as a warning in the Tygacil® (tigecycline) package insert. Acute pancreatitis may therefore be a tetracycline-class drug effect, and would be an emerging safety signal for doxycycline.

MO comment: *The safety profile of doxycyline has been well characterized over the course of its continuous clinical use over the past 48 years. Nevertheless, the reports of acute pancreatitis will be investigated as an emerging safety signal* (b)(5) (b)(5) *. A finding of drug-induced pancreatitis would not significantly alter the risk-benefit profile of the drug.*

8 Postmarket Experience

Not applicable.

9 Appendices

9.1 Literature Review/References

1. Nitya S, Deepa K, Mangaiarkkarasi A, Karthikeyan K, "Doxycycline induced generalized bullous fixed drug eruption - A case report." J Young Pharm. 2013 Dec;5(4):195-6.
2. Lebrun-Vignes B, Kreft-Jais C, Castot A, Chosidow O; French Network of Regional Centers of Pharmacovigilance, "Comparative analysis of adverse drug reactions to tetracyclines: results of a French national survey and review of the literature." Br J Dermatol. 2012 Jun;166(6):1333-41.
3. Pasricha, JS "Drugs causing fixed eruptions." Br J Dermatol. 1979 Jul;100:183–185
4. Moy BT, Kapila N. "Probable doxycycline-induced acute pancreatitis." Am J Health Syst Pharm. 2016 Mar 1;73(5):286-91.
5. Wachira JK, Jensen CH, Rhone K. "Doxycycline-induced pancreatitis: A rare finding." S D Med 2013;66(6):227-9.
6. Inayat F, Virk HU, Yoon DJ, Riaz I. "Drug-induced pancreatitis: A rare manifestation of doxycycline administration." NAJMS. 2016; 8:117-120.
7. Ocal S, Selçuk H, Korkmaz M, Unal H, Yilmaz U. "Acute pancreatitis following doxycycline and ornidazole coadministration." JOP. 2010 Nov 9;11(6):614-6.

8. Eland IA, van Puijenbroek EP, Sturkenboom MJ, et al. “Drug-associated acute pancreatitis: Twenty-one years of spontaneous reporting in the Netherlands.” Am J Gastroenterol 1999;94(9):2417-22.
9. Nicolau DP, Mengedoht DE, Kline JJ. “Tetracycline-induced pancreatitis.” Am J Gastroenterol. 1991 Nov;86(11):1669-71
10. Gilson M, Moachon L, Jeanne L, et al. “Acute pancreatitis related to tigecycline: Case report and review of the literature.” Scand J Infect Dis 2008;40:681-3.

9.2 Labeling Recommendations

Draft labeling has been submitted and will be reviewed separately.

9.3 Advisory Committee Meeting

No advisory committee was deemed necessary for this efficacy supplement.

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

/s/

EDWARD A WEINSTEIN
05/13/2016

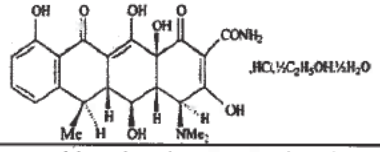
YULIYA I YASINSKAYA
05/13/2016

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

50-795/S-22

PRODUCT QUALITY REVIEW

CHEMIST'S REVIEW # 1	1. ORGANIZATIO **HFD-520 DAIP**	2. NDA Number(s) 50-795
3. Name and Address of Applicant (City & State): Mayne Pharma International Pty Ltd. 1538 Main North Road Salisbury South, South Australia 5106 Australia US Agent: Metrics, Inc. 1240 Sugg Parkway Greenville, NC 27834		4. AF No. 5. Supplement(s) Number(s) Date(s) SCS/022 13-Jul-2015
6. Drug Name: Doryx® (b)(4)	7. Nonproprietary Name: Doxycycline Hyclate Delayed-Release Tablets, USP	8. Amendments & Other (reports, etc.) - Dates
9. Supplement Provides For: addition of a modified formulation and two corresponding new product strengths, 60 mg and 120 mg.		
10. Pharmacological Category: Antimicrobial	11. How Dispensed: : Rx	12. Related IND(s)/ NDA(s)/DMF(s)
13. Dosage Form(s): Tablets, Delayed-Release	Potency(ies): 50, 75, 80, 100, 150, 200 mg	
14. Chemical Name: Doxycycline hyclate, USP, $(C_{22}H_{24}N_2O_8 \cdot HCl)_2 \cdot C_2H_6O \cdot H_2O$ MW: 1025.87 *CAS #[24390-14-5]*		15. Chemical Structure: 

16. Comments: *In vitro* Dissolution tests demonstrated the currently approved Doryx tablets do release some drug in acid environment. To reduce the potential for esophageal and gastric irritation, formulation development was initiated to produce a delayed release tablet with additional *in vitro* acid resistance. This is reflected by a change in the proposed product's dissolution specification in acid media from NMT (b)(4) at 20 minutes to NMT (b)(4) at 60 minutes. Multipoint dissolution profile of the new formulation and the single-dose bioequivalence comparison studies were evaluated by Biopharm consult reviewer Banu Zolnik, Ph.D. and an approval recommendation was issued on 4/19/2016. Batch analysis results and 6 months stability data for 3 commercial batches of the proposed formulation support the approval of this supplement. The proposed labelling was assessed by DMEPA and this reviewer, some comments were sent to the applicant.

17. Conclusions and Recommendations:
From CMC perspective this supplement is recommended for approval.

CC: Original NDA 50795 HFD-520/Division File

R/D initialed by : Hasmukh Patel

17. REVIEWER	Yongde Lu Digitally signed by Yongde Lu DN: cn=Yongde Lu, o=CDER/OPQ/OLP, ou=FDA, email=yongde.lu@fda.hhs.gov, c=US Date: 2016.05.05 16:51:55 -04'00'	Date Completed: 05-May-2016
18. BRANCH CHIEF David Lewis, Ph.D. signing for Hasmukh Patel, Ph.D.	David B. Lewis -S Digitally signed by David B. Lewis -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=David B. Lewis -S, 0.9.2342.19200300.100.1.1=1300124430 Date: 2016.05.06 07:41:22 -04'00'	

Review Note

This supplement seeks approval for the addition of a modified formulation with 2 corresponding new strengths, 60 mg and 120 mg, to the currently approved Doryx® tablets (NDA 50795).

It should be noted that the modified formulation will be added as an alternative to currently approved Doryx tablets, that means it will not replace the current Doryx formulation which will remains unchanged and continue to be marketed. To avoid any confusion with Doryx tablets, the modified formulation will be marketed using a distinct trade named, proposed to be Doryx (b)(4) and will only be marketed in 60 mg and 120 mg strengths. (b)(4) (b)(4) (b)(4)

Background

The currently approved Doryx tablet formulation is a delayed-release formulation of doxycycline hyclate drug substance, where the API pellets are coated with a pH dependent polymer coating (b)(4) (b)(4)

The currently approved Doryx tablets were designed to delay the release of API until the pellets reach the higher pH environment of the small intestine. Although formulated with an increased acid resistance compared to conventional doxycycline hyclate oral formulations, *in vitro* dissolution results demonstrated that the current Doryx tablet does release some drug in acid environment. The test includes 6 approved tablet strengths: 50, 75, 80, 100, 150 and 200 mg.

Formulation development was initiated to produce a delayed release tablet with additional *in vitro* acid resistance. This is reflected by a change in the proposed product's dissolution specification in acid media to NMT (b)(4) at 60 minutes. The current dissolution specification for Doryx Tablets in acid media is NMT (b)(4) at 20 minutes.

Per FDA Guidance for Industry SUPAC-MR: Modified Release Solid Oral Dosage Forms, Doryx (b)(4) is classified as a Level 3 change involving the "Addition or deletion of release controlling excipients (e.g., release controlling polymers/plasticizers)". Accordingly, the following documentation is included in this submission:

- Updated product release specifications and executed batch records for 3 batches of each strength of Doryx (b)(4)
- Multiple dissolution profile using the application/compendial test conditions for the Doryx (b)(4) and a marketed batch (currently approved Doryx Tablets).
- Three batches with 3 months accelerated stability data with post-approval commitment for long-term stability data for the first 3 production batches to be reported in future annual report.
- A single-dose bioequivalence study comparing 1 x Doryx (b)(4) 120 mg tablet (modified formulation) with 1 x Doryx 100 mg tablet (currently approved formulation).

Description of the formulation changes

Applicant assigns a product code while products are in the development phase. Table 1 list the various product codes that have been referred to in this NDA and their corresponding supplement numbers, including current supplement for the 60 mg and 120 mg.

Table 1: Product Codes Related to NDA 50-975 and its Supplements

Product Code	Product	NDA Reference	Date Approved
(b)(4)	Doryx™ Tablet, 100 mg and 75 mg	NDA 50-795	May 6, 2005
	Doryx™ Tablet, 150 mg	Supplement S-005	June 20, 2008
	Doryx™ Tablet, 200 mg	Supplement S-010	April 11, 2013
	Doryx™ Tablet, 80 mg	Supplement S-011	April 11, 2013
	Doryx™ Tablet, 50 mg	Supplement S-019	December 19, 2014
	Doryx (b)(4) Tablet, 60 mg and 120 mg	Current supplement	----

The proposed modified formulation, Doryx (b)(4) designated with the product code MP336, is a tablet containing yellow delayed release doxycycline hyclate pellets (b)(4) presented in dose weight proportional 60 mg and 120 mg dosage strengths. The pellets are (b)(4)

(b)(4)

(b)(4)

The commercial batch size for Doryx (b)(4) is (b)(4) Apart from the formulation modification and the change in the dissolution specifications, the process and equipment for Doryx (b)(4) are unchanged from that which is currently approved for Doryx tablets.

A unit dose composition comparison of the Doryx and the Doryx (b)(4) formulations is provided below in Table 2.

Table 2: Per Unit Composition for Doryx (b)(4) Tablet, 60 & 120 mg and Doryx Tablet, 50 & 100 mg

Component	Doryx (b)(4) Tablet			Doryx Tablet		
	60 mg tablet[1] (mg/tablet)	120 mg tablet[1] (mg/tablet)	%w/w	50 mg tablet[1] (mg/tablet)	100 mg tablet[1] (mg/tablet)	%w/w
Doxycycline hyclate[2]	69.4[3]	138	(b)(4)			(b)(4)
Lactose Monohydrate						
Microcrystalline Cellulose (b)(4)						
Sodium Lauryl Sulphate						
Sodium Chloride (b)(4)						
Talc (b)(4) (b)(4)						
Lactose Anhydrous						
Starch (Corn Starch)						
Crospovidone (b)(4) (b)(4)						
Magnesium Stearate (b)(4) (b)(4)						
TOTAL						

(b)(4)

The (b)(4) of both Doryx (b)(4) and Doryx tablets (b)(4) however, the (b)(4) (b)(4) (b)(4) 2 formulations is (b)(4) as shown in Figure 1 below.

Figure 1: Illustration of formulation difference between Doryx (b)(4) and Doryx tablets

Specifications for Doryx (b)(4) 120 mg (as representative)

Except for description and drug release-acid, the release specifications for the proposed Doryx (b)(4) tablet, 60 mg and 120 mg are (b)(4) to those currently approved for Doryx Tablets, 50, 75, 80, 100, 150 and 200 mg.

Table 2: Release Specifications for Doryx [redacted] Tablet, 120 mg

Test	Specification
Description[1]	White oval tablet containing yellow pellets and debossed with "DC" on one face and plain on the other
Identification – HPLC	[redacted]
Uniformity of Dosage Units	Complies with the requirement of USP <905> for content uniformity
Content of Doxycycline	[redacted] doxycycline label claim per tablet
Related Compounds	[redacted]
Drug Release – Acid[2]	No individual value exceeds [redacted] dissolved in 60 minutes [redacted] in 60 minutes.
Drug Release – Buffer	Meet the requirements of USP <711>. [redacted] The percent of labeled amount of Doxycycline dissolved in 20 minutes: [redacted]
[redacted]	NMT [redacted]
	NMT [redacted]
	NMT [redacted]
[redacted]	

Batch analysis data

Three Doryx [redacted] Tablets, 60 mg and 120 mg exhibit batches (1022212, 1022213 and 1022214) were manufactured. The only difference between the proposed Doryx [redacted] tablets and the approved Doryx tablets is their drug release-acid profiles since the formulation for Doryx [redacted] tablets is designed to achieve increased acid resistance. Table 2 below shows the 120 mg strength tablets release data.

Table 2: Drug Product Release Testing Results for Exhibit Batches of Doryx (b)(4) Tablet, 120 mg

Specification		Lot Number		
Test	Acceptance Criteria	1022215	1022216	1022217
Description[1]	White oval tablet containing yellow pellets and debossed with "D|C" on one face and plain on the other.	Complies	Complies	Complies
Identification - HPLC	(b)(4)	Positive	Positive	Positive
Uniformity of Dosage Units	Complies with the requirement of USP <905> for content uniformity Acceptance Value: NMT (b)(4) %	(b)(4)		
Content of Doxycycline	(b)(4) of the labeled amount of doxycycline			
Related Compounds	(b)(4)			
Drug Release - Acid	Each unit is not more than (b)(4) at 60 minutes Maximum at 60 minutes NMT (b)(4)			
Drug Release - Buffer	Meet the requirements of USP <711>: The percent of labeled amount of Doxycycline dissolved in 20 minutes (Q: (b)(4) Minimum at 20 minutes NLT (b)(4) %			
(b)(4)	NMT (b)(4)			
	NMT (b)(4) %			
	NMT (b)(4) %			
	(b)(4)			

Results: All testing results met the approved release specifications.

Stability data

For the stability program (b)(4) were manufactured (b)(4) 60 mg and 120 mg Doryx (b)(4) tablets. The tablets were packaged into their various container closure systems and representative batches placed on stability as shown in Table 1 below.

Table 1: Summary of Doryx [(b)(4)] Tablets, 60 & 120 mg Stability Batches

[(b)(4)] Batch Number	Doryx [(b)(4)] Tablets		Container-Closure System					
			120-mg Tablet			60-mg Tablet		
	120 mg tablet batch number	60 mg tablet batch number	115 cc HDPE bottle	20 cc HDPE bottle	Bulk pack	70 cc HDPE bottle	20 cc HDPE bottle	Bulk pack
[(b)(4)]	1022215[1]		1022536	1022539				
		1022212				1022533	1022542	
	1022216		1022537					
		1022213					1022543	1022213
	1022217			1022541	1022217			
		1022214				1022535		

[1] clinical trial material taken from this batch

Stability specification

Table 3: Stability Specification for Doryx [(b)(4)] Tablets, 120 mg

Test	Specification	Analytical Method (Mayne method numbers)
Description	White oval tablet containing yellow pellets and debossed with "DC" on one face and plain on the other.	visual
Content of Doxycycline	[(b)(4)] of doxycycline label claim per tablet [(b)(4)]	[(b)(4)]
Related Compounds		
Drug Release – Acid	No individual value exceeds [(b)(4)] dissolved in 60 minutes. If [(b)(4)] [(D)(4)] n 60 minutes.	
Drug Release – Buffer	Meet the requirements of USP <711> [(b)(4)] The percent of labeled amount of Doxycycline dissolved in 20 minutes (Q [(b)(4)] is as follows: [(b)(4)]	
[(b)(4)]	NMT [(b)(4)]	

Testing Protocol

- Long-term conditions: 25°C/60% RH, at 0, 1, 3, 6, 9, 12, 18, 24, 36 months
- Accelerated conditions: 40°C/75% RH, at 0, 1, 3, 6 months
- Intermediate conditions: 30°C/65% RH, at 0, 1, 3, 6, 9, 12 months

Stability data

At the time of submission 6 months data were available for accelerated and long term storage conditions.

PRODUCT: MP336 60 mg DR Tablets 120's STS NUMBER: (b)(4) DATE COMMENCED: 04/12/14

PACKAGING: 70mL HDPE bott (b)(4) BATCH NUMBER: 1022533 STORAGE CONDITION: 40°C/75% RH

TEST NAME		TEST SPECIFICATION	TEST INTERVAL			
			INITIAL	1 MONTH	3 MONTHS	6 MONTHS
Description		Complies	Complies	Complies	Complies	Complies
Content of Doxycycline		(b)(4) amount of doxycycline	(b)(4)			
Related Compounds	(b)(4)	NMT (b)(4) w/w				
		NMT w/w				
		NMT w/w				
		NMT w/w				
Drug Release Acid (b)(4) 60 min	Maximum	Refer STS				
	Average	Record				
	Stage	Record				
Drug Release Buffer (b)(4) 20 min	Minimum	Refer STS				
	Average	Refer STS				
	Stage	Record				
(b)(4)						

NMT = Not More Than;
STS = Stability Trial Specification

(b)(4)

PRODUCT: MP336 60 mg DR Tablets 120's STS NUMBER: (b)(4) DATE COMMENCED: 04/12/14

PACKAGING: 70mL HDPE bottle (b)(4) BATCH NUMBER: 1022533 STORAGE CONDITION: 25°C/60% RH

TEST NAME		TEST SPECIFICATION	SAMPLE AGE								
			INITIAL	1 MONTH	3 MONTHS	6 MONTHS	9 MONTHS	12 MONTHS	18 MONTHS	24 MONTHS	36 MONTHS
Description		Complies	Complies	Complies	Complies	Complies					
Content of Doxycycline		(b)(4) of labelled amount of doxycycline	(b)(4)								
Related Compounds	(b)(4)	NMT (b)(4) w/w									
		NMT w/w									
		NMT w/w									
		NMT w/w									
Drug Release Acid (b) 60 min	Maximum	Refer STS									
	Average	Record									
	Stage	Record									
Drug Release Buffer (b) 20 min	Minimum	Refer STS									
	Average	Refer STS									
	Stage	Record									
(b)(4)		NMT (b)(4) w/w									

NMT = Not More Than;
STS = Stability Trial Specification

(b)(4)

Result: All stability test results meet the specification limits.

Shelf-life proposed

The stability of 3 batches of Doryx (b)(4) tablets, 120 mg, in commercial containers has been evaluated for 6 months. The tablets did not exhibit significant change in any tested attributes at the 6 month time point after storage at accelerated conditions. In addition, the stability test results are consistent with

results seen for approved Doryx tablets, and as such, it is expected that Doryx (b)(4) tablets, 120 mg wll likewise remain stable for **24 months**, the current approved shelf-life for Doryx tablets.

Claim for categorical exclusion of environmental assessment
In accordance with 21 CFR 25.31(a), applicant claims a categorical exclusion from the requirement to prepare an Environmental Assessment.

The proposed modified formulation and (b)(4) corresponding new dosage strengths are an alternative to the products already registered under NDA 50-795 and the products will not be administered for a longer duration or for different indications that were previously in effect. At the expected level of exposure, the substances are not expected to be toxic to organism in the environment. *Acceptable*

Biopharmaceutics consult review
The following dissolution concerns were evaluated by consult Biopharm review team:

- Multiple dissolution profile using the application/compendial test conditions for the Doryx (b)(4) and a marketed batch (currently approved Doryx Tablets).
- A single-dose bioequivalence study comparing 1 x Doryx (b)(4) 120 mg tablet (modified formulation) with 1 x Doryx 100 mg tablet (currently approved formulation).

The Biopharm assessment for above dissolution concerns has been conducted by Banu Zolnik, Ph.D. and Elsbeth Chikhale, Ph.D. who issued an **approval** recommendation for this supplement on 4/19/2016. *The applicant's biowaiver request for the 60 mg Doryx MPC tablets is granted.* See Biopharm review for details.

Labeling
- **DMEPA comments:**

Following comments from container labels and carton labeling have been forwarded to applicant.

1. Remove all references to the proprietary name, Doryx (b)(4) throughout the labels and labeling as this proposed proprietary name has been found unacceptable due to safety concerns.

2. Revise the colored box around strength statement on the proposed modified formulation carton and container labels and labeling to a color (b)(4) to mitigate product selection errors.

We note that the (b)(4) color block around the strength statement used on the 60 mg strength carton and container labels and labeling of the proposed modified formulation (b)(4) (b)(4) and the (b)(4) around the strength statement used on the 120 mg strength carton and container labels and labeling of the proposed modified formulation looks (b)(4).

(b)(4)

[redacted]

In response to DMEPA comments a revised proprietary name DORYX MPC was proposed by applicant.

- **CMC sections review**

a) Packaging Insert

HIGHLGHTS OF PRESCRIBING INFORMATION

Product Title: from: **Doryx** (b)(4) **(doxycycline hyclate delayed-release tablets), Oral use.**
changed to: **DORYX MPC (doxycycline hyclate delayed-release tablets), for oral use**

DOSAGE FORM AND STRENGTHS: from: [redacted](b)(4) (3)
Changed to: Delayed-Release Tablets: 60 mg, 120 mg (3)

FULL PRESRIBING NFORMATION: CONTENTS

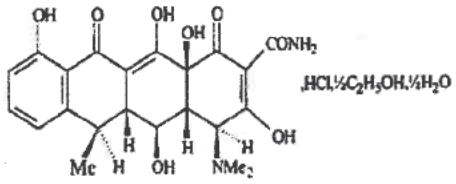
3 DOSAGE FORMS AND STRENGTHS:

Doryx [redacted](b)(4) MPC(doxycycline hyclate delayed-release tablets), 60 mg and 120 mg are white, oval tablets containing yellow pellets and debossed on one face with "D6" and "DC", respectively, and plain on the other. Each tablet contains [redacted](b)(4) doxycycline [redacted](b)(4) 60 mg or 120 mg [redacted](b)(4) (equivalent to doxycycline hyclate 69.4 mg or 138.8 mg).

11 DESCRIPTION

Doryx [redacted](b)(4) MPC (doxycycline hyclate delayed-release tablets) for oral use [redacted](b)(4) contain [redacted](b)(4) coated pellets of doxycycline hyclate, a broad-spectrum antibacterial synthetically derived from oxytetracycline, in a delayed-release formulation for oral administration.

The structural formula for doxycycline hyclate is:



with a molecular formula of $C_{22}H_{24}N_2O_8$ [redacted](b)(4) HCl, ½ C_2H_6O, ½ H_2O and a molecular weight of ~~512.9~~ 1025.88. The chemical name [redacted](b)(4) for doxycycline hyclate is [4S(4aR,5S,5aR,6R,12aS)]-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,5,10,12,12a-pentahydroxy-6-methyl-1,11-deoxonaphthacene-2-carboxamide monohydrochloride, compounded with ethyl alcohol (2:1), monohydrate. Doxycycline hyclate is a yellow crystalline powder soluble in water and in solutions of alkali hydroxides and carbonates. Doxycycline has a high degree of lipid solubility and a low affinity for calcium binding. It is highly stable in normal human serum. Doxycycline will not degrade into an epianhydro form. Inactive ingredients in the tablet formulation are: lactose monohydrate; microcrystalline cellulose; sodium lauryl sulfate; sodium chloride; talc, anhydrous lactose; corn starch; crospovidone; magnesium stearate; cellulosic polymer coating.

Each Doryx [redacted](b)(4) MPC 60 mg Tablet contains 3.6 mg (0.157 mEq) of sodium and each Doryx [redacted](b)(4) MPC 120 mg Tablet contains 7.2 mg (0.313 mEq) of sodium.

16 HOW SUPPLIED AND HANDLING

Doryx [(b)(4)] MPC (doxycycline hyclate delayed-release tablets), 60 mg and 120 mg are white, oval tablets containing yellow pellets and debossed on one face with "D6" and "DC", respectively, and plain on the other. Each tablet contains [(b)(4)] doxycycline [(b)(4)] 60 mg or 120 mg [(b)(4)] (equivalent to doxycycline hyclate 69.4 mg or 138.8 mg).

The 60 mg tablet is supplied in bottles of 120 tablets NDC xxxxx-xxx-xx

The 120 mg tablet is supplied in bottles of 60 tablets. NDC xxxxx-xxx-xx

Store at 25° C (77° F); excursions permitted to 15°C to 30° C (59°F to 86° F) [see USP Controlled Room Temperature]. Dispense in a tight, light-resistant container (USP).

B) Container label and carton labeling

Per 'salt policy' following equivalency statement is added to container and carton labels:

"Each tablet contains doxycycline 60 mg or 120 mg-(equivalent to doxycycline hyclate 69.4 mg or 138.8 mg)"

Assessment: *In vitro* Dissolution tests demonstrated the currently approved Doryx tablets do release some drug in acid environment. To reduce the potential for esophageal and gastric irritation, formulation development was initiated to produce a delayed release tablet with additional *in vitro* acid resistance. This is reflected by a change in the proposed product's dissolution specification in acid media from NMT [(b)(4)] at 20 minutes to NMT [(b)(4)] at 60 minutes. Multipoint dissolution profile of the new formulation and the single-dose bioequivalence comparison studies were evaluated by Biopharm consult review staff and an approval recommendation was issued on 4/19/2016. Batch analysis results and 6 months stability data for 3 commercial batches of the proposed formulation support the approval of this supplement. The proposed labelling was assessed by DMEPA and this reviewer, some comments were sent to the applicant.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 50-795/S-22

MICROBIOLOGY REVIEW(S)

Division of Anti-Infective Products (HFD-520)
Office of Antimicrobial Products (OND/CDER)
Clinical Microbiology Labeling Review

Date:	5/18/2016
Clinical Microbiology Reviewer:	**Simone M. Shurland**
NDA/ANDA # (Supplement #):	**50-795** (Suppl22: SDN 313, 339
Date Company Submitted:	7/13/2015, 4/1/2016
Date received by CDER:	7/13/2015, 4/7/2016
Date Assigned:	9/3/2015
Applicant Name:	Mayne Pharmaceuticals International PTY Ltd 1538 Main North Road Salisbury South, Australia 5106 Contact Person: Heike Carmichael Manager Regulatory Affairs and Product Safety Phone: +61 8 8614 7704 E-mail: heike.carmichael@maynepharma.com
Proprietary Name:	Doryx® MPC
Established Name:	Doxycycline hyclate
Dosage Form (Route of Administration):	Delayed-Release tablets (Oral)
Dosage Strength	60 mg and 120 mg
Recommended Action:	**Approvable, pending accepted version of the labeling**

EXECUTIVE SUMMARY

Doxycycline monohydrate is a semisynthetic tetracycline. Supplement#22 is a Prior Approval supplement submitted on July 13, 2015. The product marketed by the Applicant includes the 75 mg, 80 mg, 100 mg, 150 mg and 200 mg doxycycline hyclate delayed-release tablets. Each of these strengths is supplied under the tradename DORYX® which is owed by the Applicant's distributor, Warner Chilcott (now owned by Actavis). The Applicant is seeking to add a modified formulation and two corresponding new product strengths of 60 mg and 120 mg. The modified formulation will not replace the current Doryx® formulation; rather it will be added to NDA 50-795 as an alternative to the currently approved Doryx tablets. This new formulation will be marketed under the new tradename, Doryx MPC. The Applicant intention is to only supply the 60 mg and 120 mg tablet under the Doryx MPC tradename.

Division of Anti-Infective Products (HFD-520)
Office of Antimicrobial Products (OND/CDER)
Clinical Microbiology Labeling Review

This review focuses on the proposed labeling for DORYX® MPC delayed-release tablets, more specifically the microbiology section of the full prescribing. The following edits were recommended to the Applicant for the microbiology section of the labeling:

- **LIST OF MICROORGANISMS**
  - Based on the Indications and Usage section added *Listeria monocytogenes*.

- **CHANGES TO MICROBIOLOGY LABELING TEXT**
  Additions to the labeling text are shown in bold and deletions are shown in strikethrough text. Minor editorial and grammatical corrections are not specified.
  - 12.1. Mechanism of Action
    Doxycycline is a tetracycline-class (b)(4) antimicrobial (b)(4) drug [see Microbiology (12.4)].

  - Susceptibility Test Methods
    When available, the clinical microbiology laboratory should provide cumulative reports (b)(4) of *in vitro* susceptibility test results for antibacterial (b)(4) drugs used in local hospitals and practice areas (b)(4) to the physician as periodic reports that describe the susceptibility profile of nosocomial and community-acquired pathogens. These reports should aid the physician in selecting an (b)(4) antibacterial drug for treatment.

  - Diffusion Techniques
    Quantitative methods that require measurement of zone diameters can also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. (b)(4) —The zone size should be determined using a standard test method.[5,7,8] This procedure uses paper disks impregnated with 30 mcg doxycycline to test the susceptibility of bacteria to doxycycline. The disk diffusion interpretive criteria are provided in Table 1.

  - A report of Susceptible (S) indicates that the antimicrobial is likely to inhibit growth of the (b)(4) microorganism if the antimicrobial (b)(4) drug reaches the concentrations usually achievable at the site of infection (b)(4). (b)(4) A report of Intermediate (I) indicates that the result should be considered equivocal, and, if the (b)(4) microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone that prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of Resistant (R) indicates that the antimicrobial ~~drug~~ is not likely to

inhibit growth of the (b)(4) microorganism if the antimicrobial (b)(4) drug reaches the concentrations usually achievable at the infection site; other therapy should be selected.

- **REFERENCES**
  - Update the existing Clinical Laboratory Standards Institute (CLSI) references in the package insert to the most recent versions of the documents as follows:
    1. Clinical and Laboratory Standards Institute (CLSI). *Performance Standards for Antimicrobial Susceptibility Testing; Twenty-~~fourth~~ sixth Informational Supplement*, CLSI document ~~M100-S24~~ M100-S26. Clinical and Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087, USA, ~~2014~~ 2016.

SUMMARY AND RECOMMENDATIONS

The labeling is approvable pending an updated version of the labeling.

Simone M. Shurland, PhD.
Clinical Microbiology Reviewer
DAIP HFD-520
May 17, 2016

Concurrence: Kalavati Suvarna, PhD
Acting Clinical Microbiology Team Leader
5/18/2016

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

/s/

SIMONE SHURLAND
05/18/2016

KALAVATI C SUVARNA
05/18/2016

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 50-795/S-22

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

BIOPHARMACEUTICS REVIEW Office of New Drug Products - Division of Biopharmaceutics			
Application No.:	NDA 50795/ Efficacy Supplement-22	**Biopharmaceutics Reviewer:** Banu Sizanli Zolnik, Ph.D.	
Division:	Division of Anti-Infective Drug Products		
Applicant:	Mayne Pharma International Pty Ltd.	**Biopharmaceutics Lead (Acting):** Elsbeth Chikhale, Ph.D.	
Trade Name:	Doryx®	**Biopharmaceutics Branch Chief (Acting)** Angelica Dorantes, Ph.D.	
Generic Name:	Doxycycline hyclate delayed release tablets	**Date Assigned:**	07/29/2015
Indication:	Doryx® is indicated for various infections	**Date of Review:**	4/19/2016
Dosage Form/ Strength	Delayed Release Tablets/ 50 mg, 75 mg, 80 mg, 100 mg, 150 mg, and 200 mg	**Route of Administration**	Oral

SUBMISSIONS REVIEWED IN THIS DOCUMENT		
Submission date	**Date of Consult**	**PDUFA DATE**
7/20/2015	NA	5/20/2016

Type of Submission:	Efficacy Supplement
Review:	• Evaluation of dissolution data in support of the approval of the newly proposed 120 mg tablets • Evaluation of biowaiver request for the newly proposed 60 mg tablets • Evaluation for the proposed dissolution acceptance criteria for the newly proposed 60 mg and 120 mg tablets

EXECUTIVE SUMMARY

This review focuses on the evaluation of 1) multi-point dissolution profiles with the approved dissolution method to support of the approval of the proposed 120 mg Doryx® MPC tablets , 2) the biowaiver request for 60 mg Doryx® MPC tablets, and 3) the proposed dissolution acceptance criteria for the proposed 60 mg and 120 mg Doryx® MPC tablets.

- **The approval of the 120 mg strength is based on the following:**

a) An acceptable bioequivalence study comparing the proposed 120 mg strength Doryx® MPC tablets to the approved 100 mg Doryx® tablets. OCP has reviewed the BE study and found the study acceptable.
b) Multi-point dissolution profile obtained during the buffer stage using the application/compendial test conditions for the proposed Doryx® MPC 120 mg tablets and the approved Doryx® 100 mg tablets.

- **The approval of the 60 mg strength Doryx® MPC tablets is based on the following:**

  a) An acceptable bioequivalence study comparing the proposed 120 mg tablets to the approved 100 mg tablets
  b) Similarity between the dissolution profiles of the proposed 60 mg Doryx® MPC tablets and the proposed 120 mg Doryx® MPC tablets.
  c) The proposed 60 mg Doryx® MPC tablet is [redacted] (b)(4) to 120 mg Doryx® MPC tablet.

- **The following proposed dissolution method and acceptance criteria for the new 60 mg and 120 mg tablets are found acceptable:**

Acid stage dissolution specification:

Apparatus	USP Apparatus 1 (baskets), 100 rpm
Media	0.06 N hydrochloric acid
Temperature	37°C ± 0.5°C
Volume	900mL
Acceptance Criterion	Not more than [redacted] (b)(4) % in 60 minutes

Buffer stage dissolution specification:

Apparatus	USP Apparatus 1 (baskets), 100 rpm
Media	pH 5.5, neutralized phthalate buffer
Temperature	37°C ± 0.5°C
Volume	900mL
Acceptance Criterion	Q = [redacted] (b)(4) at 20 minutes

Conclusion and Recommendation:
The Applicant's biowaiver request for the 60 mg Doryx® MPC tablets is granted and **APPROVAL** is recommended for supplement 022 under NDA 50795 for Doryx® MPC tablets, 60 mg and 120 mg.

BIOPHARMACEUTICS ASSESSMENT

Background:

Doryx® (doxycycline hyclate delayed-release) tablets contain a tetracycline class antibacterial indicated for: Rickettsial infections, sexually transmitted infections, respiratory tract infections, specific bacterial infections, ophthalmic infections, anthrax, including inhalation anthrax (post-exposure), alternative treatment for selected infections when penicillin is contraindicated, adjunctive therapy in acute intestinal amebiasis and severe acne, and prophylaxis of malaria. Doryx® is currently approved as 50 mg, 75 mg, 80 mg, 100 mg, 150 mg and 200 mg strength delayed release tablets.

Submission:

In this Efficacy Supplement 22 to the original NDA 50795, the Applicant is proposing to add two new strengths (60 mg and 120 mg) with **a modified** formulation. The Applicant submitted a single dose bioequivalence study (single dose, two-period, two treatment, two sequence cross over design) comparing the proposed 120 mg strength tablets and the approved 100 mg Doryx® tablets (BE study was evaluated by OCP) in this Efficacy Supplement. The Applicant has requested a biowaiver for the proposed 60 mg strength tablets.

The currently approved Doryx® tablets were designed to delay the release of doxycycline hyclate from the pellets by coating the pellets with a pH dependent polymer coating. Although the approved delayed release tablets are formulated using an acid resistant coating, in vitro dissolution results show that approved Doryx® tablets release a substantial amount of drug in acid (for example (b)(4)% of the drug is released in 60 minutes in 0.06 N HCl). Because of the association between drug release in acid and the potential esophageal and gastric irritation, the Applicant stated that they have developed an alternative delayed release formulation.

The Applicant stated that the proposed 60 mg and 120 mg tablets with the modified formulation will not replace the current 50 mg and 100 mg Doryx® tablets; rather the new strengths will be added to NDA 50795 as an alternative under the Doryx® MPC trade name. It is emphasized in the submission that the currently approved Doryx® tablets will remain unchanged and will be continued to be marketed. It should be noted that previously an alternative name Dorxy® (b)(4) was proposed by the Applicant in this Supplement 22; however this name was not accepted by DMEPA. The trade name Doryx® MPC is found conditionally acceptable by DMEPA.

Review:

This review focuses on the evaluation of 1) multi-point dissolution profiles using the approved dissolution method to support of the approval of the proposed 120 mg Doryx® MPC tablets , 2) the biowaiver request for 60 mg Doryx® MPC tablets, and 3) the proposed dissolution acceptance criteria for the proposed 60 mg and 120 mg Doryx® MPC tablets.

Approved *In Vitro* Dissolution Method and Acceptance criteria

The currently approved in vitro dissolution test for Doryx® tablets consists of two stages:
1) Drug Release – Acid, and
2) Drug Release – at pH 5.5 buffer

The Drug Release – Acid test confirms the functionality of the pH dependent pellet coating. The Drug Release – Buffer (pH 5.5) test confirms drug release from the Doryx® tablets. The test methods and acceptance criteria are summarized below in Table 1 and Table 2 (refer to the Biopharmaceutics Review dated 03/04/2011 by Dr. John Duan).

Table 1 Drug Release – Acid method and acceptance criterion

Apparatus	USP Apparatus 1 (baskets), 100 rpm
Media	0.06 N hydrochloric acid
Temperature	37°C ± 0.5°C
Volume	900mL
Sampling Time	20 minutes
Analytical Method	(b)(4)
Number of Tablets	per USP <724 >
Acceptance criterion	No individual value exceeds (b)(4) dissolved. (b)(4) (b)(4) (b)(4) in 20 minutes

Table 2 Drug Release – Buffer method and acceptance criterion

Apparatus	USP Apparatus 1 (baskets), 100 rpm
Media	pH 5.5, neutralized phthalate buffer
Temperature	37°C ± 0.5°C
Volume	900mL
Sampling Time	20 minutes
Analytical Method	(b)(4)
Number of Tablets	per USP <724>
Acceptance criterion	Q = (b)(4) at 20 minutes, USP <724>

Drug Product

Table 3 below shows the description and composition of the proposed 60 mg and 120 mg tablets as well as approved Doryx® tablets, 50 and 100 mg.

Table 3 Composition of Doryx® MPC and Doryx® Tablets

(b)(4)

Component	Doryx Tablet			Doryx Tablet		
	60 mg tablet (mg/tablet)	120 mg tablet (mg/tablet)	%w/w	50 mg tablet (mg/tablet)	100 mg tablet (mg/tablet)	%w/w
Doxycycline hyclate[2]	69.4[3]	138				
Lactose Monohydrate						
Microcrystalline Cellulose						
Sodium Lauryl Sulphate						
Sodium Chloride						
Talc						
Lactose Anhydrous						
Starch (Corn Starch)						
Crospovidone						
Magnesium Stearate						
TOTAL						

(b)(4)

Dissolution data supporting the approval of the 120 mg strength tablets

Per the FDA guidance for Industry SUPAC MR, the proposed change in formulation for the Dorxy® is classified as a Level 3 change under Section VI-C Component and Composition – Release of Controlling Excipient involving addition or deletion of release controlling excipient. The approval of the 120 mg strength is based on the following:

a) An acceptable bioequivalence study comparing the proposed 120 mg strength Doryx® MPC tablets to the approved 100 mg Doryx® tablets. It is noted that the 200 mg strength Doryx® tablet is the reference listed drug identified in the Orange Book (OCP has reviewed the BE study and found the study acceptable. Refer to the OCP review in DARRTS dated 3/10/2016 by Dr. Dakshina Chilukuri).
b) Multi-point dissolution profile obtained during the buffer stage using the application/compendial test conditions for the proposed Doryx® MPC 120 mg tablets and the approved Doryx® - 100 mg tablets.

The Applicant provided comparative dissolution data between the proposed 120 mg and the approved 100 mg strengths Doryx® tablets using the approved dissolution method (0.06N HCL stage and pH 5.5 buffer stage) as well as in pH 1.2, pH 4.5 and pH 6.8 media.

Comparative dissolution data in the approved dissolution method-Acid Stage

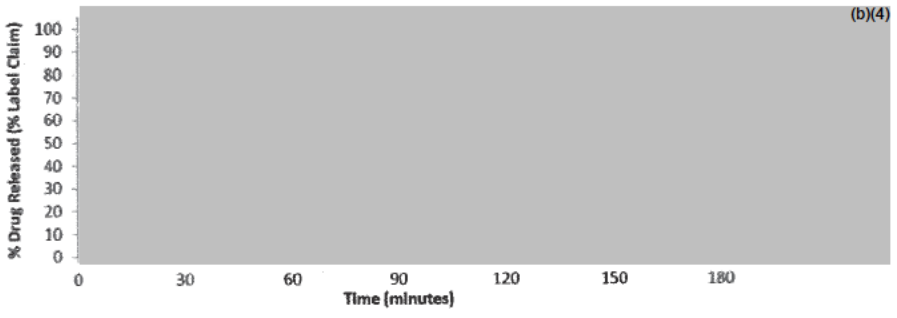
Table 4 Summary of In Vitro Dissolution Studies in Acid Stage 120 mg vs 100 mg

Dissolution Conditions	Apparatus:	USP Apparatus I (basket)
	Speed of Rotation:	100RPM
	Medium:	Acid: 0.06N Hydrochloric Acid
	Volume:	900 mL
	Temperature:	37° ± 0.5°C
Firm's Proposed Specifications	Acid: No individual value exceeds (b)(4) dissolved in 60 minutes	
Dissolution Testing Site (Name, Address)	Mayne Pharma International Pty Ltd 1538 Main North Road Salisbury South, SA 5106	

Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (minutes) 10	20	30	45	60	90	120	180	Study Report Location
Study Report #:N/A	Nov 2014	Test Product A Batch No. 1022536 Manufacture Date: Oct 2014	120 mg Tablet	12	Mean	0.7	1.8	3.0	5.1	7.9	21.5	40.1	58.4	N/A
					Range	(b)(4)								
					%CV	24.2	12.1	10.2	8.1	6.5	3.5	2.3	2.1	
Study Report #:N/A	Feb 2014	Reference Product B Batch No. 980334 Expiration Date: Dec 2015	100 mg Tablet	12	Mean	2.8	9.9	33.6	85.5	97.7	101.5	102.3	102.7	
					Range	(b)(4)								
					%CV	14.1	6.4	3.6	2.9	2.7	2.6	2.6	2.7	

Reference Table 28 and Table 29 for individual values at each time point.

Figure 1 Comparison of drug release between 120 mg Doryx® MPC (batch 1022215) and 100 mg Doryx® (batch 980334) Tablets in Acid Stage



Comparative dissolution data in the approved dissolution method-Buffer Stage

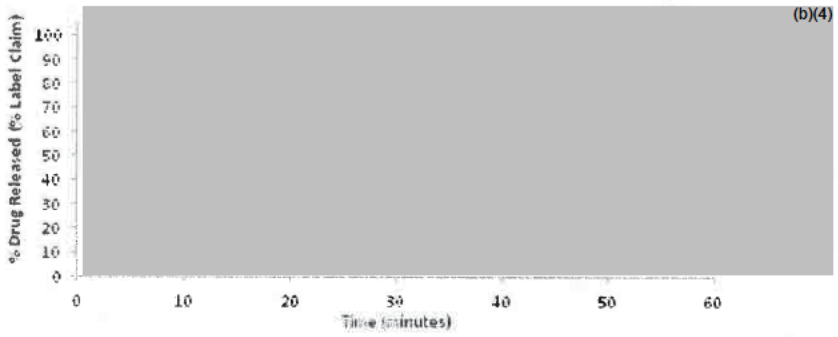
Table 5 Summary of In Vitro Dissolution Studies in Buffer Stage 120 mg vs 100 mg

Dissolution Conditions	Apparatus:	USP Apparatus I (basket)
	Speed of Rotation:	100RPM
	Medium:	Buffer: pH 5.5 Phthalate Buffer
	Volume:	900 mL
	Temperature:	37° ± 0.5°C
Firm's Proposed Specifications	Buffer: Percent of labeled amount of doxycycline dissolved in 20 minutes (Q= (b)(4)	
Dissolution Testing Site (Name, Address)	Mayne Pharma International Pty Ltd 1538 Main North Road Salisbury South, SA 5106	

Study Ref No.	Testing Date	Product ID \ Batch No (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (minutes) 5	10	15	20	30	45	60	Study Report Location
Study Report #:N/A	Nov 2014	Test Product A Batch No. 1022536 Manufacture Date: Oct 2014	120 mg Tablet	12	Mean	33.9	70.3	90.2	97.4	99.7	99.8	99.8	N/A
					Range	(b)(4)							
					%CV	26.9	6.1	3.7	3.6	4.1	4.1	4.1	
Study Report #:N/A	Feb 2014	Reference Product B Batch No. 980334 Expiration Date: Dec 2015	100 mg Tablet	12	Mean	25.5	67.2	84.3	95.5	100.5	101.0	101.1	
					Range	(b)(4)							
					%CV	9.4	5.1	4.6	4.4	3.7	3.8	3.8	

Reference Table 30 and Table 31 for individual values at each time point

Figure 2 Comparison of drug release between 120 mg Doryx® MPC (batch 1022215) and 100 mg Doryx® (batch 980334) Tablets in Buffer Stage



Comparative dissolution data in pH 1.2

Table 6 Summary of In Vitro Dissolution Studies in pH 1.2 Medium 120 mg vs 100 mg

Dissolution Conditions			**Apparatus:**	**USP Apparatus I (basket)**										
			Speed of Rotation:	**100RPM**										
			Medium:	**pH 1.2**										
			Volume:	**900 mL**										
			Temperature:	**37° ± 0.5°C**										
Firm's Proposed Specifications			For comparative purposes only, dissolution in this medium is not part of the proposed specifications											
Dissolution Testing Site (Name, Address)			Mayne Pharma International Pty Ltd 1538 Main North Road Salisbury South, SA 5106											
Study Ref No.	**Testing Date**	**Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times (minutes)**								**Study Report Location**
						10	**20**	**30**	**45**	**60**	**90**	**120**	**180**	
Study Report #:N/A	Nov 2014	Test Product A Batch No. 1022536 Manufacture Date: Oct 2014	120 mg Tablet	12	Mean	0.8	1.8	2.8	4.6	6.9	17.8	34.7	51.7	N/A
					Range	(b)(4)								
					%CV	16.4	9.8	7.3	8.0	6.4	4.0	2.8	2.2	
Study Report #:N/A	Feb 2014	Reference Product B Batch No. 980334 Expiration Date: Dec 2015	100 mg Tablet	12	Mean	2.3	7.8	23.7	71.9	90.4	98.0	100.1	101.4	
					Range	(b)(4)								
					%CV	15.8	9.9	5.4	1.5	2.0	2.6	2.1	2.2	

Reference Table 36 and Table 37 for individual values at each time point.

Comparative dissolution data in pH 4.5

Table 7 Summary of In Vitro Dissolution Studies in pH 4.5 Medium 120 mg vs 100 mg

Dissolution Conditions			**Apparatus:**	**USP Apparatus I (basket)**										
			Speed of Rotation:	**100RPM**										
			Medium:	**pH 4.5**										
			Volume:	**900 mL**										
			Temperature:	**37° ± 0.5°C**										
Firm's Proposed Specifications			For comparative purposes only, dissolution in this medium is not part of the proposed specifications											
Dissolution Testing Site (Name, Address)			Mayne Pharma International Pty Ltd 1538 Main North Road Salisbury South, SA 5106											
Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (minutes)								Study Report Location
						10	20	30	45	60	90	120	180	
Study Report #:N/A	Nov 2014	Test Product A Batch No. 1022536 Manufacture Date: Oct 2014	120 mg Tablet	12	Mean	0.2	0.9	1.8	3.9	9.3	21.7	33.8	49.1	N/A
					Range	(b)(4)								
					%CV	47.8	14.7	8.9	4.5	4.4	2.7	2.4	2.5	
Study Report #:N/A	Feb 2014	Reference Product B Batch No. 980334 Expiration Date: Dec 2015	100 mg Tablet	12	Mean	3.1	21.9	58.4	88.6	74.0	82.4	88.6	95.7	
					Range	(b)(4)								
					%CV	10.6	5.7	2.1	2.0	2.0	1.9	1.9	1.9	

Reference Table 38 and Table 39 for individual values at each time point

Comparative dissolution data in pH 6.8

Table 8 Summary of In Vitro Dissolution Studies in pH 6.8 Medium 120 mg vs 100 mg

Dissolution Conditions	**Apparatus:**	USP Apparatus I (basket)
	Speed of Rotation:	100RPM
	Medium:	pH 6.8
	Volume:	900 mL
	Temperature:	37° ± 0.5°C
Firm's Proposed Specifications	For comparative purposes only, dissolution in this medium is not part of the proposed specifications	
Dissolution Testing Site (Name, Address)	Mayne Pharma International Pty Ltd 1538 Main North Road Salisbury South, SA 5106	

Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (minutes) 15	30	45	60	Study Report Location
Study Report #:N/A	Nov 2014	Test Product A Batch No. 1022536 Manufacture Date: Oct 2014	120 mg Tablet	12	Mean	99.6	99.8	99.7	99.7	N/A
					Range	(b)(4)				
					%CV	2.4	2.3	2.3	2.3	
Study Report #:N/A	Feb 2014	Reference Product B Batch No. 980334 Expiration Date: Dec 2015	100 mg Tablet	12	Mean	102.9	102.7	102.8	102.9	
					Range	(b)(4)				
					%CV	2.4	2.4	2.4	2.4	

Reference Table 40 and Table 41 for individual values at each time point

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Reviewer's Assessment:

The newly proposed 120 mg Doryx® MPC tablets exhibit a lower drug release in the acid stage (b)(4) drug released in 60 minutes for the proposed 120 mg strength vs. (b)(4) drug released in 60 minutes for the approved 100 mg strength tablets). Both formulations exhibited overlapping drug release profiles in the buffer stage. As expected, both formulations showed differences in drug release in pH 1.2 and pH 4.5 buffers, while drug release was similar in pH 6.8 buffer. Therefore, the provided comparative dissolution data supports the approval of the newly proposed 120 mg strength Doryx® MPC tablets.

1) The dissolution data supporting the request to waive the requirement for conducting a bioequivalence study for the 60 mg strength Doryx® MPC tablets.

The approval of the 60 mg strength Doryx® MPC tablets is based on the following:

a) An acceptable bioequivalence study comparing the proposed 120 mg strength to the approved 100 mg tablet
b) Similarity between the dissolution profiles of the proposed 60 mg Doryx® MPC tablets and the proposed 120 mg Doryx® MPC tablets.
c) The proposed 60 mg Doryx® MPC tablet is (b)(4) 120 mg Doryx® MPC tablet. Both strengths are manufactured (b)(4) the strengths is (b)(4)

The Applicant provided comparative dissolution data between 60 mg and 120 mg strengths in the approved dissolution method (0.06N HCL and pH 5.5 buffer stages) as well as pH 1.2, pH 4.5 and pH 6.8 media. The Applicant also provided comparative dissolution data between the proposed 60 mg and the approved 50 mg strengths, which are not reviewed here since the approval of the 60 mg strength rely on the comparative dissolution data between the 120 mg and 60 mg strength.

Comparative dissolution data in the approved dissolution method-Acid Stage 120 mg vs 60 mg

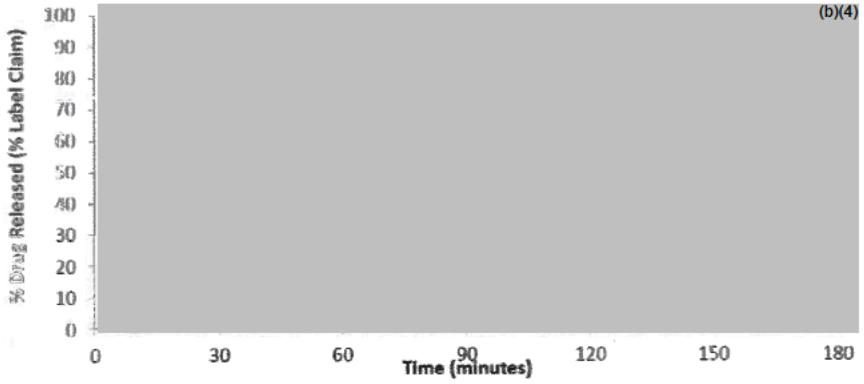
Table 9 Summary of In Vitro Dissolution Studies in Acid Stage 120 mg vs 60 mg

Dissolution Conditions	**Apparatus:**	USP Apparatus I (basket)
	Speed of Rotation:	100RPM
	Medium:	Acid: 0.06N Hydrochloric Acid
	Volume:	900 mL
	Temperature:	37° ± 0.5°C
Firm's Proposed Specifications		Acid: No individual value exceeds (b)(4) dissolved in 60 minutes
Dissolution Testing Site (Name, Address)		Mayne Pharma International Pty Ltd 1538 Main North Road Salisbury South, SA 5106

Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (minutes) 10	20	30	45	60	90	120	180	Study Report Location
Study Report #N/A	Nov 2014	Test Product Batch No. 1022536 Manufacture Date: Oct 2014	120 mg Tablet	12	Mean	0.7	1.8	3.0	5.1	7.9	21.5	40.1	58.4	N/A
					Range	(b)(4)								
					%CV	24.2	12.1	10.2	8.1	6.5	3.5	2.3	2.1	
Study Report #N/A	Nov 2014	Test Product Batch No. 1022212 Manufacture Date: Oct 2014	60 mg Tablet	12	Mean	0.8	1.8	2.9	5.0	7.7	21.7	40.1	59.4	
					Range	(b)(4)								
					%CV	35.5	21.0	17.2	15.2	12.8	6.0	4.5	3.6	

Reference Table 28 and Table 32 for individual values at each time point.

Figure 3 Comparison of drug release between 120 mg Doryx® MPC (batch 1022215) and 60 mg Doryx® MPC (batch 1022212) Tablets in Acid Stage



Comparative dissolution data in the approved dissolution method-Buffer Stage 120 mg vs 60 mg

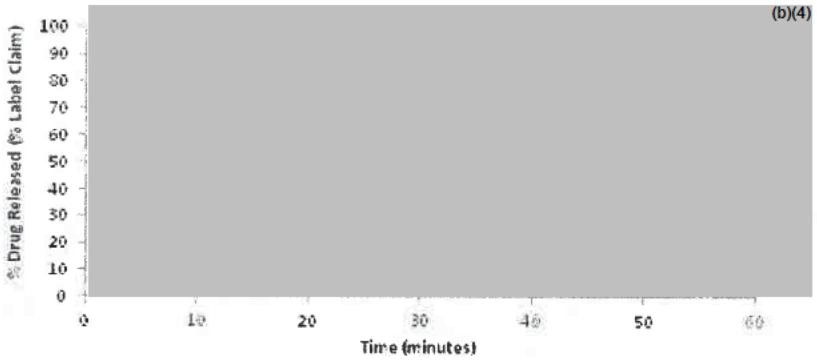
Table 10 Summary of In Vitro Dissolution Studies in Buffer Stage 120 mg vs 60 mg

Dissolution Conditions	**Apparatus:**	USP Apparatus I (basket)
	Speed of Rotation:	100RPM
	Medium:	Buffer: pH 5.5 Phthalate Buffer
	Volume:	900 mL
	Temperature:	37° ± 0.5°C
Firm's Proposed Specifications	Buffer: Percent of labeled amount of doxycycline dissolved in 20 minutes (Q= (b)(4)	
Dissolution Testing Site (Name, Address)	Mayne Pharma International Pty Ltd 1538 Main North Road Salisbury South, SA 5106	

Study Ref No.	Testing Date	Product ID \ Batch No. (Test – Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (minutes) 5	10	15	20	30	45	60	Study Report Location
Study Report #:N/A	Nov 2014	Test Product Batch No. 1022536 Manufacture Date: Oct 2014	120 mg Tablet	12	Mean	33.9	70.3	90.2	97.4	99.7	99.8	99.8	N/A
					Range	(b)(4)							
					%CV	26.9	6.1	3.7	3.6	4.1	4.1	4.1	
Study Report #:N/A	Nov 2014	Test Product Batch No. 1022212 Manufacture Date: Oct 2014:	60 mg Tablet	12	Mean	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	
					Range	(b)(4)							
					%CV	26.8	7.4	4.1	3.6	4.2	4.3	4.2	

Reference Table 30 and Table 34 for individual values at each time point

Figure 4 Comparison of drug release between 120 mg Doryx® MPC (batch 1022215) and 60 mg Doryx® MPC (batch 1022212) Tablets in Buffer Stage



Comparative dissolution data in pH 1.2 (120 mg vs 60 mg)

Table 11 Summary of In Vitro Dissolution Studies in pH 1.2 Medium 120 mg vs 60 mg

Dissolution Conditions	**Apparatus:**	USP Apparatus I (basket)
	Speed of Rotation:	100RPM
	Medium:	pH 1.2
	Volume:	900 mL
	Temperature:	37° ± 0.5°C
Firm's Proposed Specifications	For comparative purposes only, dissolution in this medium is not part of the proposed specifications	
Dissolution Testing Site (Name, Address)	Mayne Pharma International Pty Ltd 1538 Main North Road Salisbury South, SA 5106	

Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (minutes) 10	20	30	45	60	90	120	180	Study Report Location
Study Report #:N/A	Nov 2014	Test Product Batch No. 1022536 Manufacture Date: Oct 2014	120 mg Tablet	12	Mean	0.8	1.8	2.8	4.6	6.9	17.8	34.7	51.7	N/A
					Range	(b)(4)								
					%CV	16.4	9.8	7.3	8.0	6.4	4.0	2.8	2.2	
Study Report #:N/A	Nov 2014	Test Product Batch No. 1022212 Manufacture Date: Oct 2014	60 mg Tablet	12	Mean	1.1	2.2	3.3	5.1	7.3	18.4	35.5	52.3	
					Range	(b)(4)								
					%CV	50.9	29.6	23.6	19.5	16.3	7.5	5.4	5.0	

Reference Table 36 and Table 42 for individual values at each time point.

Comparative dissolution data in pH 4.5 (120 mg vs 60 mg)

Table 12 Summary of In Vitro Dissolution Studies in pH 4.5 Medium 120 mg vs 60 mg

Dissolution Conditions	**Apparatus:**	USP Apparatus I (basket)
	Speed of Rotation:	100RPM
	Medium:	pH 4.5
	Volume:	900 mL
	Temperature:	37° ± 0.5°C
Firm's Proposed Specifications	For comparative purposes only, dissolution in this medium is not part of the proposed specifications	
Dissolution Testing Site (Name, Address)	Mayne Pharma International Pty Ltd 1538 Main North Road Salisbury South, SA 5106	

Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (minutes) 10	20	30	45	60	90	120	180	Study Report Location
Study Report #:N/A	Nov 2014	Test Product Batch No. 1022536 Manufacture Date: Oct 2014	120 mg Tablet	12	Mean	0.2	0.9	1.8	3.9	9.3	21.7	33.8	49.1	N/A
					Range	(b)(4)								
					%CV	47.8	14.7	8.9	4.5	4.4	2.7	2.4	2.5	
Study Report #:N/A	Nov 2014	Test Product Batch No. 1022212 Manufacture Date: Oct 2014	60 mg Tablet	12	Mean	0.2	1.0	1.9	4.1	7.6	22.6	35.4	51.6	
					Range	(b)(4)								
					%CV	87.5	30.7	21.6	14.0	10.8	7.2	6.1	6.0	

Reference Table 38 and Table 44 for individual values at each time point

Comparative dissolution data in pH 6.8 (120 mg vs 60 mg)

Table 13 Summary of In Vitro Dissolution Studies in pH 6.8 Medium 120 mg vs 60 mg

Dissolution Conditions	**Apparatus:**	USP Apparatus I (basket)
	Speed of Rotation:	100RPM
	Medium:	pH 6.8
	Volume:	900 mL
	Temperature:	37° ± 0.5°C
Firm's Proposed Specifications	For comparative purposes only, dissolution in this medium is not part of the proposed specifications	
Dissolution Testing Site (Name, Address)	Mayne Pharma International Pty Ltd 1538 Main North Road Salisbury South, SA 5106	

Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (minutes) 15	30	45	60	Study Report Location
Study Report #:N/A	Nov 2014	Test Product Batch No. 1022536 Manufacture Date: Oct 2014	120 mg Tablet	12	Mean	99.6	99.8	99.7	99.7	N/A
					Range	(b)(4)				
					%CV	2.4	2.3	2.3	2.3	
Study Report #:N/A	Nov 2014	Test Product Batch No. 1022212 Manufacture Date: Oct 2014	60 mg Tablet	12	Mean	102.9	102.9	102.8	102.8	
					Range	(b)(4)				
					%CV	2.8	2.8	2.9	2.9	

Reference Table 40 and Table 46 for individual values at each time point

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Reviewer's Assessment:

Drug release profiles are similar between the proposed 60 mg and 120 mg strength Doryx® MPC tablets in the approved dissolution method-acid and buffer stage as well as pH 1.2, 4.5 and 6.8 buffers. Therefore, the provided comparative dissolution data supports the biowaiver request for the 60 mg strength Doryx® MPC tablets.

2) Evaluation for the proposed dissolution acceptance criterion in the acid stage

The Applicant proposes a dissolution acceptance criterion of no more than (b)(4) at 60 minutes for both newly proposed strengths (60 mg and 120 mg) in the acid stage. The approved dissolution acceptance criterion for Doryx® tablets (50, 75, 80, 100, 150, and 200 mg) in acid media is not more than (b)(4) at 20 minutes.

The Applicant is proposing the same approved dissolution acceptance criterion in the buffer stage (Q= (b)(4) at 20 minutes) for the newly proposed 60 mg and 120 mg strengths.

Table 14 Summary of Drug Release-Acid Method and Acceptance Criterion for Dorxy® and Doryx® MPC (refered to as MP336 tablets)

Parameter	Method/Specification Details	
Dosage Form	MP336 tablets	Doryx tablets
Strength	60 & 120 mg	50, 75 , 80, 100, 150 & 200 mg

Parameter	Method/Specification Details	
Apparatus	USP Apparatus 1 (baskets), 100 rpm	USP Apparatus 1 (baskets), 100 rpm
Media	0.06 N hydrochloric acid, 37°C	0.06 N hydrochloric acid, 37°C
Volume	900 mL	900 mL
Sampling Time	60 minutes	20 minutes
Analytical Method	(b)(4)	
Number of Tablets	per USP <724 >	per USP <724 >
Specification	No individual value exceeds (b)(4) dissolved. (b)(4) (b)(4) (b)(4) (b)(4) in 60 minutes	No individual value exceeds (b)(4) dissolved. (b)(4) (b)(4) in 20 minutes

Reviewer's Assessment:
The Applicant's proposed dissolution acceptance criteria for the newly proposed 60 mg and 120 mg Doryx® MPC tablets (not more than (b)(4) in 60 minutes in the acid stage and Q= (b)(4) in 20 minutes in the buffer stage) are **acceptable** based on the provided dissolution data.

RECOMMENDATION
The Biopharmaceutics team reviewed the supporting data for the approval of the 120 mg strength Doryx® MPC tablets and the biowaiver request for the 60 mg strength Doryx® MPC tablets.

From Biopharmaceutics perspective, the Applicant's biowaiver request for the 60 mg Doryx® MPC tablets is granted and **APPROVAL** is recommended for supplement 022 under NDA 50795 for Doryx® MPC tablets, 60 mg and 120 mg.

Banu S. Zolnik -S

Digitally signed by Banu S. Zolnik -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Banu S. Zolnik -S, 0.9.2342.19200300.100.1.1=1300438310
Date: 2016.04.19 11:56:56 -04'00'

Banu Sizanli Zolnik, Ph. D.
Biopharmaceutics Reviewer
Division of Biopharmaceutics
Office of New Drug Products
Office of Product Quality

Elsbeth G. Chikhale -A

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Date: 2016.04.19 12:18:03 -04'00'

Elsbeth Chikhale, Ph.D.
Acting Biopharmaceutics Lead
Division of Biopharmaceutics
Office of New Drug Products
Office of Product Quality

cc: Angelica Dorantes, Ph.D.

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/s/

JONATHAN T DOW
05/24/2016

CLINICAL PHARMACOLOGY REVIEW ADDENDUM

NDA(s): 50-795/S-022	Submission Date(s): 07/20/2015
Drug/Strengths	DORYX MPC™ tablet (Doxycycline)/ 60 mg and 120 mg
OCP Reviewer	Dakshina M. Chilukuri, PhD
OCP Team Leader	Seong H. Jang, PhD
OCP Division	DCP4
OND Division	DAIP
Applicant	Mayne Pharma
Formulation/Strength	Doryx® (doxycycline hyclate delayed-release tablets) 50 mg, 75 mg, 80 mg, 100 mg, 150 mg and 200 mg
Indication(s)	Rickettsial infections, sexually transmitted infections, respiratory tract infections, specific bacterial infections, ophthalmic infections, anthrax, including inhalational anthrax (post-exposure), alternative treatment for selected infections when penicillin is contraindicated, adjunctive therapy in acute intestinal amebiasis and severe acne, prophylaxis of malaria

This Addendum to the original Clinical Pharmacology review for DORYX®, filed in the DARRTS on 03/10/2016, is to indicate that the bioanalytical site (b)(4) (b)(4) was not inspected as part of this NDA review. Email communications with the Office of Study Integrity and Surveillance (OSIS) indicated that this site has been inspected on several other previous occasions and no issues were identified with these previous inspections. The most recent inspection of the site was conducted by OSIS in (b)(4) and this inspection was found to be acceptable. Thus, the bioanalytical and PK results of the BE trial conducted as part of this NDA should be deemed acceptable.

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/s/

DAKSHINA M CHILUKURI
05/16/2016

SEONG H JANG
05/16/2016

CLINICAL PHARMACOLOGY REVIEW

NDA(s): 50-795/S-022	Submission Date(s): 07/20/2015
Drug/Strengths	DORYX MPC™ tablet (Doxycycline)/ 60 mg and 120 mg
OCP Reviewer	Dakshina M. Chilukuri, PhD
OCP Team Leader	Seong H. Jang, PhD
OCP Division	DCP4
OND Division	DAIP
Applicant	Mayne Pharma
Formulation/Strength	Doryx® (doxycycline hyclate delayed-release tablets) 50 mg, 75 mg, 80 mg, 100 mg, 150 mg and 200 mg
Indication(s)	Rickettsial infections, sexually transmitted infections, respiratory tract infections, specific bacterial infections, ophthalmic infections, anthrax, including inhalational anthrax (post-exposure), alternative treatment for selected infections when penicillin is contraindicated, adjunctive therapy in acute intestinal amebiasis and severe acne, prophylaxis of malaria

1. EXECUTIVE SUMMARY

This sNDA from Mayne Pharma International Pty Ltd (Mayne Pharma) is for FDA approval of an additional modified formulation (currently named as DORYX MPC™ tablet) and two corresponding new drug product strengths of 60 mg and 120 mg. Mayne Pharma had submitted this as a prior approval supplement (PAS) seeking to add a modified formulation and two corresponding new drug product strengths of 60 mg and 120 mg. This modified formulation will not replace the current Doryx™ formulation; rather it will be added to NDA 50-795 as an alternative to the currently approved Doryx™ tablets. The currently approved Doryx™ tablets will remain unchanged and will continue to be marketed. To avoid any confusion with Doryx™ tablets, the modified formulation will be marketed using a distinct trade name, proposed to be Doryx MPC™, only available as distinct tablet strengths (60 mg and 120 mg).

The currently approved Doryx™ tablet formulation described in NDA 50-795 is a delayed-release formulation of doxycycline hyclate, where doxycycline hyclate pellets are coated with a pH dependent polymer coating (b) (4) The currently approved Doryx™ tablets were designed to delay the release of doxycycline hyclate until the pellets reach the higher pH environment of the small intestine. Results of the *in vitro* dissolution test, Drug Release Acid, confirmed that drug release from Doryx™ tablets was delayed in acid. NDA 50-795 includes six approved tablet strengths: 50, 75, 80, 100, 150 and 200 mg.

This efficacy supplement was submitted by the applicant and contains the following information.

- An updated product release specifications and executed batch records for three batches of each strength of Doryx MPC™. A multipoint dissolution profile during the

buffer stage of testing using the application/compendial test conditions for the modified formulation drug product, Doryx MPC™, and a marketed batch (currently approved drug product, Doryx™ Tablets).

- Three batches of the modified formulation drug product with at least three months' accelerated stability data along with a Post-Approval Stability Commitment for long-term stability data for the first three production batches to be reported in the subsequent annual report.
- A single-dose bioequivalence study (Study 11450707) comparing 1 x Doryx MPC™120 mg tablet (modified formulation drug product) with 1 x Doryx™ 100 mg tablet (currently approved drug product). Note: although the Orange Book identifies the Doryx™ 200 mg tablet as the Reference Listed Drug, the Doryx™ 100 mg tablet was used as the comparator in the submitted biostudy as: (i) the Doryx™ 100 mg strength tablet was expected to be directly bioequivalent to the Doryx MPC™120 mg tablet, and (ii) NDA 50-795 already contains biostudies demonstrating the bioequivalence of 2 x Doryx™ 100 mg tablets versus 1 x Doryx™ 200 mg tablets.
- The applicant has requested a full waiver of the requirement for conducting bioequivalence studies for the Doryx MPC™ Tablet 60 mg based on the acceptable bioavailability study conducted on the 120-mg strength tablet, the calculated f2 dissolution values for the Doryx MPC™ 60-mg and 120-mg strength tablets indicating similar dissolution profiles and the fact that the 60-mg tablet is a dose proportional lower strength variant of the 120-mg strength tablet. The waiver request will be reviewed by Dr. Banu Zolnik at ONDP.

Study 11450707 was conducted as an open-label study to evaluate the relative bioavailability of a single dose of the Test formulation, (b)(4) Doxycycline Hyclate Delayed-Release (DR) Tablets, 120 mg compared to a single dose of the Reference formulation, (b)(4) Doxycycline Hyclate Delayed-Release Tablets USP, 100 mg, in healthy adult subjects under fasted conditions. For the natural log-transformed data for doxycycline, the 90% confidence intervals on the geometric mean test-to-reference ratios for AUC_t, AUC_∞, and C_{max}, fell within the standard bioequivalence range of 80.00-125.00%. Therefore, the test formulation of doxycycline hyclate 120 mg DR Tablet (manufactured by Mayne Pharma International Pty. Ltd.) was demonstrated to be bioequivalent to the reference formulation, doxycycline hyclate delayed-release tablets,

Doryx MPC™ Tablets contain 20% more administered drug but achieves a comparable rate and extent of exposure from a Doryx™ Tablets. The benefit/risk assessment of Doryx MPC remains favorable given the reduced potential for gastric irritation. In addition, the proposed dosing instructions for the Doryx MPC™ Tablets are well within the approved dosing window of the Doryx™ Tablet, which includes a 200 mg dose strength.

The BE study conducted by the applicant was reviewed and it is agreed that the test formulation of Doxycycline Hyclate Delayed-Release Tablets, 120 mg meets the 90% CI criterion for log transformed AUC_{0-t}, AUC_{0-inf}, and C_{max} and, therefore, has shown equivalent bioavailability to a similar dosage of the Reference formulation, Doxycycline Hyclate Delayed-Release Tablets USP, 100 mg.

2. RECOMMENDATIONS

The clinical pharmacology information provided by the applicant in support of the 505 (b)(2) application is found to be acceptable and supports the approval of Doryx MPC™ pending the review of the biowaiver request and an agreement on the labeling.

Individual Study Review

STUDY NO. 11450707

STUDY TITLE:
Study to Evaluate the Relative Bioavailability of a Test Formulation of Doxycycline Hyclate Delayed-Release Tablets, 120 mg (Mayne) compared to Doxycycline Hyclate Delayed-Release Tablets USP, 100 mg (Mayne) in Healthy Adult Subjects under Fasted Conditions

OBJECTIVE: The objective of this study was to evaluate the relative bioavailability of a test formulation of MP336 (doxycycline) 120 mg DR Tablet (manufactured by Mayne Pharma International Pty. Ltd.) compared to the marketed reference product, doxycycline hyclate delayed-release tablets, USP 100 mg (manufactured by: Mayne Pharma International Pty. Ltd.; distributed by: (b) (4) in healthy adult male and female subjects under fasted conditions.

METHODOLOGY: This was an open-label, randomized, single-dose, two-period, two-treatment, two-sequence, crossover study under fasted conditions comparing the test and reference products. The study was conducted with 28 healthy adult subjects in accordance with Protocol No. 11450707. In each period of the study, a single doxycycline hyclate delayed-release tablet (100 mg or 120 mg) was administered to subjects following an overnight fast of at least 10 hours. The test product was MP336 (doxycycline) 120 mg DR Tablet (manufactured by Mayne Pharma International Pty. Ltd.) and the reference product was doxycycline hyclate delayed-release tablets, USP 100 mg (manufactured by: Mayne Pharma International Pty. Ltd.; distributed by: (b) (4) Subjects received the test product in one of the study periods and the reference product in the other study period according to a two-sequence randomization schedule. Subjects were confined at the clinical facility from at least 10 hours before dosing until after the 24-hour blood sample collection in each study period and returned to the clinical facility for blood sample collections at 36, 48, 72, and 96 hours after dosing. The interval between doses was 14 days.

Blood samples were collected pre-dose and at intervals over 96 hours after dosing in each study period.

Pharmacokinetic and statistical analyses were performed by (b) (4) to compare the bioavailability of the test formulation relative to that of the reference product. Equivalent bioavailability was evaluated by a statistical comparison of the natural log-transformed data for the pharmacokinetic parameters AUC_{0-t}, AUC_{0-inf}, and C_{max} for doxycycline.

STATISTICAL METHODS: Twenty-two (22) blood samples were collected from each subject during each period of the study: up to 60 minutes before dosing (0 hr), and then at 0.5, 1.0, 1.5, 2.0, 2.33, 2.67, 3.0, 3.33, 3.67, 4.0, 4.5, 5.0, 6.0, 8.0, 12.0, 16.0, 24.0, 36.0*, 48.0*, 72.0*, and 96.0* hours (*return samples) post-dose for measurement of plasma doxycycline concentrations. The analytical data were used to estimate the pharmacokinetic parameters: AUC_{0-t}, AUC_{0-inf}, C_{max}, T_{max}, K_{el} and $T_{½}$ for doxycycline. The t in AUC_{0-t} is the time at which

the last measurable concentration was recorded. The Statistical Analysis System (SAS®, Version 9.4) was used for all pharmacokinetic and statistical calculations.

Analyses of Variance were performed on untransformed pharmacokinetic parameters C_{max}, AUC_{0-t}, AUC_{0-inf}, $T_{½}$, K_{el}, T_{max} and ln-transformed C_{max}, AUC_{0-t}, AUC_{0-inf} using the General Linear Model (GLM) procedure of SAS with hypothesis testing for treatment effects at $\alpha = 0.05$. The statistical model contained main effects of sequence, subject within sequence, treatment, and period. Sequence effects were tested at the 0.10 level of significance against the Type III mean square term for subjects within sequence. All other main effects were tested against the mean squared error term. Least squares means for the treatments, the differences between adjusted treatment means, and the standard errors associated with these differences were estimated.

Confidence intervals (90%) on the geometric mean ratios (obtained from logarithmic transformed data) for AUC_{0-t}, AUC_{0-inf} and C_{max} for the comparison of the test formulation to the reference product were constructed to test two one-sided hypotheses at the $\alpha = 0.05$ level of significance.

Evaluation of equivalence was based on the ln-transformed data for doxycycline. If the 90% confidence intervals on the geometric mean test-to-reference ratios for ln-transformed AUC_{0-t}, AUC_{0-inf}, and C_{max} fell within the range of 80.00-125.00%, then the test formulation was considered equivalent to the reference formulation.

Bioanalytical Analysis: The bioanalytical analysis was conducted at (b) (4)

SUMMARY OF RESULTS:

Bioanalytical Validation: The following section details the bioanalytical method validation for the analysis of doxycycline in human EDTA plasma samples. The methodology employs a protein precipitation procedure followed by UPLC-MS/MS analysis. The method was validated on an (b) (4) based LC-MS/MS system (b) (4) LC/MS/MS (b) (4) and has the following performance characteristics.

Information Requested	Data
Bioanalytical method validation report location	(b) (4) validation report (b) (4)
Analyte	Doxycycline
Internal standard (IS)	Doxycycline-d3
Method description	(b)(4)
Limit of quantitation	0.100 µg/mL
Average recovery of drug (%)	69.0%
Average recovery of IS (%)	69.2%
Standard curve concentrations (units/mL)	0.100, 0.150, 0.250, 0.600, 1.50, 4.00, 8.00, and 10.0 µg/mL
QC concentrations (units/mL)	0.100, 0.200, 0.400, 1.00, 2.50, and 7.50 µg/mL
QC Intraday precision range (%)	1.27 to 9.54%

QC Intraday accuracy range (%)	-13.1 to 9.69%
QC Interday precision range (%)	6.31 to 10.4%
QC Interday accuracy range (%)	-2.90 to 0.986%
Bench-top stability (hrs)	26 hours at room temperature (analyzed in Run (b)(4)
Stock stability (days)	Doxycycline: 34 days at 2 to 8 C in methanol (analyzed in (b)(4) - (b)(4) Doxycycline-d3: 3 days at 2 to 8 C in methanol (analyzed in Run (b)(4)
Processed stability (hrs)	196 hours at 2 to 8 C (analyzed in Run (b)(4)
Freeze-thaw stability (cycles)	Five cycles thawed at room temperature, frozen at -20 C and -70 C (analyzed in Run (b)(4)
Long-term storage stability (days)	59 days at -20 C in sodium heparin (analyzed in Run (b)(4)
Dilution integrity	1.00 µg/mL diluted five-fold 20.0 µg/mL diluted ten-fold 20.0 µg/mL diluted 20-fold
Selectivity	No interfering peaks noted in blank plasma samples

Pharmacokinetic Results: Mean plasma concentration versus time plots (linear) is presented below for doxycycline. The mean test-to-reference ratios and their associated 90% confidence intervals are provided in Table 1.

Figure 1. Mean Concentration versus Time Plot (Linear): Doxycycline

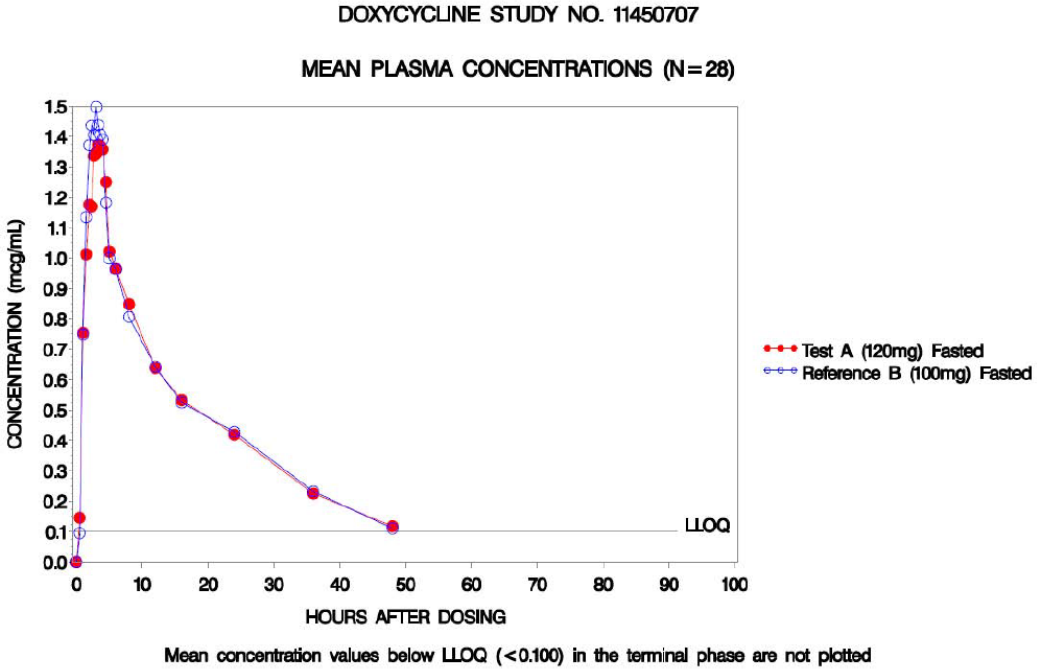

Table 1. Summary of Study Results Based on Plasma Doxycycline Concentrations

Parameter	Trt	# Datasets	LS Geometric Mean	Contrast (# subjects)	LSGM Ratio (%)	90% Confidence Interval (%)	ISCV(%)	P-value Period	P-value Sequence	BE Outcome
AUC_{0-t} (mcg·hr/mL)	A	28	22.09	A vs B (n=28)	100.67	91.66-110.56	20.8	0.6584	0.7953	Pass
	B	28	21.94							
$AUC_{0-\infty}$ (mcg·hr/mL)	A	28	25.60	A vs B (n=28)	100.43	92.18-109.42	19.0	0.4716	0.9227	Pass
	B	28	25.49							
C_{max} (mcg/mL)	A	28	1.512	A vs B (n=28)	98.68	89.38-108.95	22.0	0.6367	0.9624	Pass
	B	28	1.532							

CONCLUSION: For the natural log-transformed data for doxycycline, the 90% confidence intervals on the geometric mean test-to-reference ratios for AUC and C_{max}, fell within the standard bioequivalence range of 80.00-125.00%. Therefore, the test formulation of doxycycline hyclate 120 mg DR Tablet (manufactured by Mayne Pharma International Pty. Ltd.) was demonstrated to be bioequivalent to the reference formulation, doxycycline hyclate delayed-release tablets, USP 100 mg (manufactured by: Mayne Pharma International Pty. Ltd.; distributed by: (b) (4) under fasted conditions in healthy adult subjects.

A comparison of the time to (the observed) peak concentration (T_{max}) was assessed between the test and reference products. A nonparametric analysis revealed that no statistically significant period or carryover effect was identified. As the 90% CI for treatment effect contained 0, the test and reference products were demonstrated to be equivalent for T_{max}.

There were no serious adverse events reported during the study.

Reviewer's Comments: *The results of this study are acceptable. It is to be noted that the doses of the test and reference treatments are different (120 mg and 100 mg, respectively).*

Proposed package insert: Available separately.

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/s/

DAKSHINA M CHILUKURI
03/10/2016

SEONG H JANG
03/10/2016

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 50-795/S-22

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	April 28, 2016
Requesting Office or Division:	Division of Anti-Infective Products (DAIP)
Application Type and Number:	NDA 050795/S-022
Product Name and Strength:	Doryx MPC (doxycycline hyclate) Delayed-release Tablets, 60 mg and 120 mg
Submission Date:	December 23, 2015
Applicant/Sponsor Name:	Mayne Pharma International PTY LTD
OSE RCM #:	2016-123
DMEPA Primary Reviewer:	Deborah Myers, RPh, MBA
DMEPA Team Leader:	Vicky Borders-Hemphill, PharmD

1 PURPOSE OF MEMO

The Division of Anti-Infective Products (DAIP) requested that we review the revised container labels and carton labeling for Doryx MPC (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[1]

2 CONCLUSION & RECOMMENDATIONS

We acknowledge the receipt of the revised trade container labels, sample container labels, and sample carton labeling submitted to the Agency on December 23, 2015 and find these changes made in response to our recommendations made during our previous label and labeling review[1] acceptable from a medication error perspective.

[1] Sheppard, J. Label and Labeling Review for Doryx (b)(4) (NDA 050795). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2015 OCT 13. 14 p. OSE RCM No.: 2015-1687.

We identified additional areas of the label and labeling that can be revised to increase clarity, improve readability, and add important information to mitigate medication errors and promote the safe use of Doryx MPC. We provide recommendations in Sections 2.1 and 2.2 below and advise these are implemented prior to the approval of this NDA.

Our review notes that the National Drug Code (NDC) numbers on the container label, carton labeling, and in Section 16, *How Supplied/Storage and Handling* of the Full Prescribing Information (FPI), are currently denoted by placeholders. We request that the Sponsor submit the NDC number for this product for our review.

During the Internal Doryx MPC Labeling Review Meeting on April 25, 2016 at 1:00 pm, a statement was developed to be added as the first bullet point under Section 2.1 *Usual Dosage and Administration*; "Doryx MPC is not substitutable on a mg per mg basis with other oral doxycylines." This statement is to also be added to the Highlights of Prescribing Information. DMEPA concurs with these changes to help decrease the risk of wrong strength errors. DMEPA recommends, for consistency, that these changes be added to the Doryx Prescribing Information, as well.

In addition, during this meeting the statement, "Do not chew or crush tablets." which currently appears on the principal display panel (PDP) of the container label and carton labeling, was also added as a bullet point under Section 2.1, *Usual Dosage and Administration* for consistency. DMEPA concurs with this addition to help decrease the risk of wrong technique medication errors.

Regarding the current statement that appears on the PDP of the container label and carton labeling, and in section 3 (Dosage Forms and Strengths), section 11 (Description), and section 16 (*How Supplied/Storage and Handling*) of the FPI, [redacted] (b)(4) DMEPA informed and defers to the Office of Pharmaceutical Quality (OPQ) to determine that this statement is correct, as an appropriate equivalency statement, or if instead this statement needs to be updated.

We note that currently there is no statement included on the PDP to alert dispensers to the fact that Doryx MPC is not substitutable on a mg per per basis with other oral doxycyclines. We request that this be added to help decrease the risk of wrong strength medication errors.

2.1 RECOMMENDATIONS FOR THE DIVISION

A. Full Prescribing Information, Section 16, *How Supplied/Storage and Handling*

1. As currently presented, the NDC is denoted by a placeholder (XXXXX-XXX-XX). Since the NDC number on the container labels submitted is also denoted by a placeholder

(XXXXX-XXX-XX), we will request that the Sponsor submit the NDC number for this product for our review with the next container label revision.

2.2 RECOMMENDATIONS FOR MAYNE PHARMA INTERNATIONAL PLY LTD

All Container Labels and Carton Labeling

1. As currently presented, the NDC is denoted by a placeholder (XXXXX-XXX-XX). Add the intended NDC number to the labels and labeling and submit for our review.
2. If space permits consider adding the statement, "Doryx MPC is not substitutable on a mg per mg basis with other oral doxycylines." to the principal display panel (PDP) of both the container label and carton labeling to help decrease the risk of wrong strength medication errors.

APPENDIX A. LABEL AND LABELING SUBMITTED ON DECEMBER 23, 2015

Trade Container Labels

(b)(4)

Sample Container labels

Sample Carton labeling


(b)(4)

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/s/

DEBORAH E MYERS
04/28/2016

BRENDA V BORDERS-HEMPHILL
04/28/2016

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	October 13, 2015
Requesting Office or Division:	Division of Anti-Infective Products (DAIP)
Application Type and Number:	NDA 050755/S-022
Product Name and Strength:	Doryx (b)(4) 60 mg, 120 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Mayne Pharmaceuticals
Submission Date:	July 20, 2015
OSE RCM #:	2015-1687
DMEPA Primary Reviewer:	Jacqueline Sheppard, PharmD
DMEPA Team Leader:	Vicky Borders-Hemphill, PharmD

1 REASON FOR REVIEW

Mayne Pharmaceuticals submitted an efficacy supplement (NDA 050795/S-022) proposing to add a modified formulation and two corresponding strength to the Doryx product line. This review evaluates the proposed container labels and Prescribing Information (PI) for Doxycycline Hyclate delayed release tablets, 60 mg and 120 mg for areas of vulnerability that may lead to medication errors in response to a request from the Division of Anti-Infective Products (DAIP).

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C – N/A
ISMP Newsletters	D
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS for label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Mayne Pharmaceuticals submitted an efficacy supplement proposing to add a modified formulation and two corresponding strength to the Doryx product line. The proposed modified formulation will not replace the current Doryx formulation and will be added to the existed NDA as an alternative to the currently approved product. We reviewed the PI and proposed carton and container labels and labeling for the proposed modified formulation and evaluated them for safety and clarity.

In Section 2.1 (Dosage and Administration), (b) (4)

(b) (4) We also recommend that the PI include a non-interchangeability statement in both Section 2 (Dosage and Administration) and in the Highlights of the PI. These changes are added to DAIP's working version of PI that is currently undergoing revision (see Appendix G).

We also reviewed the container labels for the other approved strengths in the product line and compared them to the labeling for the proposed 60 mg and 120 mg strength. We note that the (b) (4) color block around the (b)(4) statement used on the 60 mg strength carton and container labels and labeling of the proposed modified formulation (b)(4) (b)(4) and the (b) (4) color block around the (b)(4) statement used on the 120 mg strength carton and container labels and labeling of the proposed modified formulation (b)(4). We recommend revising the colored box around strength statement on the proposed modified formulation carton and container labels and labeling to a color that is (b)(4) in the Doryx product line to mitigate product selection errors.

Additionally, we recommend the removal of all references to the proprietary name, Doryx (b)(4) throughout the labels and labeling as this has been found unacceptable due to safety concerns.

4 CONCLUSION & RECOMMENDATIONS

The proposed labels and labeling for proposed modified formulation may be improved to communicate important dosing information and to improve readability of important administration information. We recommend the following revisions be implemented prior to the approval of this efficacy supplement.

4.1 RECOMMENDATIONS FOR THE DIVISION

We have made revisions to the Full Prescribing Information for review and consideration by DAIP (Appendix G). These changes are added to DAIP's working version of PI that is currently undergoing revision.

4.2 RECOMMENDATIONS FOR MAYNE PHARMACEUTICALS

We recommend the following be implemented prior to approval of this NDA supplement:

A. All Container Labels and Carton Labeling

1. Remove all references to the proprietary name, Doryx (b)(4) throughout the labels and labeling as this proposed proprietary name has been found unacceptable due to safety concerns.

2. Revise the colored box around strength statement on the proposed modified formulation carton and container labels and labeling to a color that is (b)(4)

[redacted] in the product line to mitigate product selection errors. We note that the [redacted] color block around the strength statement used on the 60 mg strength carton and container labels and labeling of the proposed modified formulation [redacted] and the [redacted] color block around the strength statement used on the 120 mg strength carton and container labels and labeling of the proposed modified formulation [redacted].

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for TRADENAME that Mayne Pharmaceuticals submitted on July 20, 2015.

Table 2. Relevant Product Information for TRADENAME	
Initial Approval Date	N/A
Active Ingredient	Doxycycline Hyclate
Indication	treatment or prophylaxis of the following conditions or diseases: rickettsial infections, sexually transmitted infections, respiratory tract infections, specific bacterial infections, ophthalmic infections, anthrax, adjunctive therapy for acute intestinal amebiasis and severe acne, and prophylaxis of malaria
Route of Administration	Oral
Dosage Form	Delayed Release Tablet
Strength	60 mg, 120 mg
Dose and Frequency	Adults: 240 mg on the first day of treatment (administered 120 mg every 12 hours) followed by a maintenance dose of 120 mg daily. The maintenance dose may be administered as a single dose or as 60 mg every 12 hours. In the management of more severe infections (particularly chronic infections of the urinary tract), 120 mg every 12 hours is recommended Pediatric: The recommended dosage schedule for children weighing 45 kg or less is 5.3 mg/kg of body weight divided into two doses on the first day of treatment, followed by 2.6 mg/kg of body weight given as a single daily dose or divided into two doses on subsequent days. For more severe infections up to (b) (4) mg/kg of body weight may be used. For children over 45 kg, the usual adult dose should be used
How Supplied	60 and 120 count bottles
Storage	Controlled Room Temperature

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On October 6, 2015, we searched the L: drive and AIMS using the terms, Doryx and Doryx (b)(4) to identify reviews previously performed by DMEPA.

B.2 Results

Our search identified 12 previous reviews[1][2][3][4][5][6][7][8][9][10][11][12], and we confirmed that our previous name and labeling recommendations were considered or implemented.

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[1] Holquist C. Citizen Petition Response for Doryx (NDA 050795). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2012 Jan 27. RCM No.: 2011-3940.

[2] Holmes L. Labeling Review for Doryx (NDA 050795). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2011 Sep 6. RCM No.: 2011-1137.

[3] Holmes L. Label and Labeling Review for Doryx (NDA 050795). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2011 Jun 6. RCM No.: 2011-1137.

[4] Holmes L. Label and Labeling Review for Doryx (NDA 050795). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2011 May 4. RCM No.: 2011-557.

[5] Holmes L. Label and Labeling Review for Doryx (NDA 050795). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2010 Apr 22. RCM No.: 2010-120.

[6] Sheppard J. Label and Labeling Review for Doxteric (NDA 050795). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2015 Feb 9. RCM No.: 2015-123.

[7] Sheppard J. Proprietary Name Review for Doxteric (NDA 050795). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2014 Dec 12. RCM No.: 2014-42197.

[8] Sheppard J. Label and Labeling Memo for Doxteric (NDA 050795). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2014 Dec 5. RCM No.: 2014-1903-01.

[9] Sheppard J. Label and Labeling Review for Doxteric (NDA 050795). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2014 Oct 24. RCM No.: 2014-1903.

[10] Sheppard J. Proprietary Name Review for (b)(4) (NDA 050795). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2014 Oct 9. RCM No.: 2014-26010.

[11] Sheppard J. Label and Labeling Review for Doryx (NDA 050795). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2015 Sept 17. RCM No.: 2015-1758.

[12] Sheppard J. Label and Labeling Review for Doryx (NDA 050795). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2015 Oct 6. RCM No.: 2015-1758-01.

APPENDIX D. ISMP NEWSLETTERS

D.1 Methods

On September 4, 2015, we searched the Institute for Safe Medication Practices (ISMP) newsletters using the criteria below, and then individually reviewed each newsletter. We limited our analysis to newsletters that described medication errors or actions possibly associated with the label and labeling.

ISMP Newsletters Search Strategy	
ISMP Newletter(s)	Acute Care, Community, Nursing
Search Strategy and Terms	Match Exact Word or Phrase: Doryx, Doryx (b)(4)

D.2 Results

There were no results found that were relevant to this review.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[13] along with postmarket medication error data, we reviewed the following TRADENAME and Doryx labels and labeling submitted by Mayne Pharmaceuticals on July 28, 2015, and September 25, 2015.

- Container label
- Carton labeling
- Professional Sample Labels
- Prescribing Information

G.2 Label and Labeling Images

(b) (4)

[13] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

JACQUELINE E SHEPPARD
10/13/2015

BRENDA V BORDERS-HEMPHILL
10/13/2015

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 50-795/S-22

PROPRIETARY NAME REVIEW

PROPRIETARY NAME REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	March 14, 2016
Application Type and Number:	NDA 050795
Product Name and Strength:	Doryx MPC (doxycycline hyclate) Delayed-release Tablets, 60 mg and 120 mg
Product Type:	Single-Ingredient Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Mayne Pharma
Panorama #:	2016-2442722
DMEPA Primary Reviewer:	Deborah Myers, RPh, MBA
DMEPA Team Leader:	Vicky Borders-Hemphill, PharmD

Reference ID: 3935555

Contents

Reference ID: 3935555

1 INTRODUCTION

This review evaluates the proposed proprietary name, Doryx MPC, from a safety and misbranding perspective. The sources and methods used to evaluate the proposed name are outlined in the reference section and Appendix A, respectively. The Applicant did not submit an external name study for this proposed proprietary name.

1.1 REGULATORY HISTORY

The Applicant previously submitted the proposed proprietary name, Doryx (b)(4) on July 15, 2015. However, the Division of Medication Error Prevention and Analysis (DMEPA) found the name, Doryx (b)(4) unacceptable due to the use of the modifier, (b)(4) with the root name Doryx for this formulation, in OSE Review #2015-996751, dated October 13, 2015[1]. The proposed modifier and its intended meaning of (b)(4) (b)(4) was not supported by the overall data submitted and DMEPA had concerns that (b)(4) could be misinterpreted as demonstrated in the FDA Prescription Simulation Study.

Thus, the Applicant submitted the name, Doryx MPC, for review on December 24, 2015.

1.2 PRODUCT INFORMATION

The following product information is provided in the December 24, 2015 proprietary name submission.

Table 1. Relevant Product Information for Doryx MPC and Doryx

Product Name	**Doryx MPC**	**Doryx**
Initial Approval Date	N/A	July 21, 2004 (tablet)
Active Ingredient	Doxycycline Hyclate	Doxycyline Hyclate
Proposed Pronunciation	dor -x M P C	dor -x
Indication	Treatment or prophylaxis of the following conditions or diseases: rickettsial infections, sexually transmitted infections, respiratory tract infections, specific bacterial infections, ophthalmic infections, anthrax, alternative treatment for selected infections when penicillin is contraindicated, adjunctive therapy for acute intestinal amebiasis and severe acne, and prophylaxis of malaria	
Route of Administration	Oral	Oral

[1] Sheppard, J. Proprietary Name Review for Doryx (b)(4) NDA 050795. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2015 OCT 13. RCM No.: 2015-996751.

Table 1. Relevant Product Information for Doryx MPC and Doryx		
Product Name	**Doryx MPC**	**Doryx**
Dosage Form	Delayed-release Tablet	Delayed-release Tablet
Strengths	60 mg and 120 mg	50 mg, 75 mg, 80 mg, 100 mg, 150 mg, and 200 mg
Dose and Frequency	Adults: 240 mg on the first day of treatment (administered 120 mg every 12 hours) followed by a maintenance dose of 120 mg daily. The maintenance dose may be administered as a single dose or as 60 mg every 12 hours. In the management of more severe infections (particularly chronic infections of the urinary tract), 120 mg every 12 hours is recommended. Pediatric: The recommended dosage schedule for children weighing 45 kg or less is 5.3 mg/kg of body weight divided into two doses on the first day of treatment, followed by 2.6 mg/kg of body weight given as a single daily dose or divided into two doses on subsequent days. For more severe infections up to (b)(4) mg/kg of body weight may be used. For children over 45 kg, the usual adult dose should be used.	Adults: 200 mg on the first day of treatment (administered 100 mg every 12 hours) followed by a maintenance dose of 100 mg daily. The maintenance dose may be administered as a single dose or as 50 mg every 12 hours. In the management of more severe infections (particularly chronic infections of the urinary tract), 100 mg every 12 hours is recommended. Pediatric: The recommended dosage schedule for children weighing 45 kg or less is 4.4 mg/kg of body weight divided into two doses on the first day of treatment, followed by 2.2 mg/kg of body weight given as a single daily dose or divided into two doses on subsequent days. For more severe infections up to 4.4 mg/kg of body weight may be used. For children over 45 kg, the usual adult dose should be used.
How Supplied	60 and 120 count bottles	60 and 120 count bottles
Storage	Controlled Room Temperature	Controlled Room Temperature

2 RESULTS

The following sections provide information obtained and considered in the overall evaluation of the proposed proprietary name.

2.1 MISBRANDING ASSESSMENT

The Division of Anti-Infective Products (DAIP) did not initially concur with OPDP's and DMEPA's assessments that the proposed name would not misbrand the proposed product. Instead, the DAIP expressed concerns that the modifier and its intended meaning is promotional and that there is no in vivo data to correlate in vitro findings. Additionally,

the Office of Pharmaceutical Quality (OPQ) reviewer indicated that the Modified Polymer Coat provides additional acid resistance in vitro but it is not known if it functions the same way in-vivo, which should be used to determine if the modifier is acceptable or promotional. We note that the Applicant indicated in their submission that the modifier, "MPC", in their proposed proprietary name is intended to mean "Modified Polymer Coat" and did not make reference to acid resistance properties of the formulation. DMEPA re-queried OPDP to determine if their original promotional assessment has changed based on this concern. OPDP determined that they have no further comments and maintain their non-objection and further stated that "The acronym MPC (modified polymer coat) does not, on its own, evoke any promotional concern. As far as the in-vitro and in-vivo correlation, we think that is something too far removed from the proprietary name for it to potentially mislead healthcare providers."

After further discussion with DAIP, the review division deferred to OPDP.

2.2 SAFETY ASSESSMENT

The following aspects were considered in the safety evaluation of the name.

2.2.1 United States Adopted Names (USAN) Search

There is no USAN stem present in the proprietary name[2].

2.2.2 Components of the Proposed Proprietary Name

The proprietary name, Doryx MPC, is comprised of a two words, the root name "Doryx" and the modifier "MPC". The Applicant indicated in their submission that the modifier, "MPC", in their proposed proprietary name is intended to mean "Modified Polymer Coat".

DMEPA previously assessed the appropriateness of the root name, Doryx, in OSE Review #2015-996751, dated October 13, 2015[1]. An updated search of the FAERS database (January 22, 2016) did not identify any new cases of name confusion with Doryx. Our previous finding regarding use of the root name, Doryx has not changed.

We assess the appropriateness of the proposed modifier in Section 2.2.2.1 below.

2.2.2.1 Safety Assessment of the Modifier, MPC

The Applicant proposes the use of a modifier, "MPC", which is not a modifier with established meaning in the market. The modifier is intended to differentiate the new formulation from the original delayed release formulation. The Applicant indicates that the modifier "MPC" is intended to mean "Modified Polymer Coat." They further state that "the proposed formulation has been designed to provide additional *in vitro* acid resistance through the use of the modified polymer coat."

We note that the addition of a modifier provides some differentiation from the currently marketed product, Doryx. Additionally, the modifier may signal to health care

[2] USAN stem search conducted on January 13, 2016.

practitioners that this product differs from the currently marketed Doryx delayed release product, which may reduce the potential for medication errors.

We recognize there are limitations to this approach since the omission or oversight of modifiers in prescribing, dispensing, and administration has been cited as a source of error, particularly for those drugs that use modifiers to distinguish between members of the same product line[3]. However, we note that if this were to occur with Doryx MPC, the lack of overlapping strengths and doses between Doryx MPC and Doryx (Doryx MPC proposed strengths of 60 mg and 120 mg vs. Doryx currently available in 50 mg, 75 mg, 80 mg, 100 mg, 150 mg, and 200 mg) will likely minimize the risk for the incorrect product being dispensed. Additionally, the doses of Doryx MPC proposed are not easily achievable with the strengths available for Doryx and vice versa. Given the fact that both products are available in multiple strengths, it is unlikely that this information would be omitted on a prescription. In the event this was to occur, it would require that a pharmacist seek clarification of the intended strength, which minimizes the risk of the incorrect product being dispensed.

Although Mayne Pharmaceuticals did not provide any data to support that healthcare professionals and consumers understand the meaning of the term "MPC" and would not confuse it with another commonly used modifier, we note there is not a precedent for a meaning associated with MPC that would contribute to confusion on the market. Although the Applicant proposes the modifier to signify "Modified Polymer Coat", in the absence of a known meaning, the modifier will serve to indicate there is a difference between two products as discussed above. Additionally, our simulated prescription studies results showed that no practitioners misinterpreted the modifier "MPC" with another currently marketed modifier (see Appendix B).

Based on the totality of information considered above, we find the use of the proposed modifier, "MPC", acceptable for this product.

2.2.3 FDA Name Simulation Studies

Seventy-seven practitioners participated in DMEPA's prescription studies. The responses did not overlap with any currently marketed products nor did the responses sound or look similar to any currently marketed products or any products in the pipeline. Appendix B contains the results from the verbal and written prescription studies.

2.2.4 Comments from Other Review Disciplines at Initial Review

In response to the OSE, January 15, 2016 e-mail, the review team expressed concerns relating to the proposed proprietary name at the initial phase of the review. These concerns included; MPC can stand for Meperidine, Promethazine, and Chlorpromazine, the Modified Polymer Coat provides additional acid resistance *in-vitro* but we don't know if it functions the same way *in-vivo,* we need to understand this before we decide if MPC is an acceptable modifier, and to eliminate potential confusion we will need to

[3] Lesar TS. Prescribing Errors Involving Medication Dosage Forms. *J Gen Intern Med.* 2002; 17(8): 579-587.

develop a clear equivalency statement for the insert labeling, as well as the container labels. See our discussion of the misbranding concerns in Section 2.1 above. Our review of commonly used references did not identify MPC as an established acronym for Meperidine, Promethazine, and Chlorpromazine, instead the recognized acronym is DPT representing the brand names Demerol, Phenergan, and Thorazine. Additionally the American Academy of Pediatrics published a statement in 1995 discouraging the use of these agents as sedatives in children[4]. Additionally, DMEPA will work closely with the review team on label and labeling interventions, including an equivalency statement, to further reduce the risk for confusion and medication errors with this product. DMEPA will evaluate the labels and labeling under separate cover in OSE Review # 2016-123.

2.2.5 Medication Error Data Selection of Cases

We searched the FDA Adverse Event Reporting System (FAERS) database using the strategy listed in Table 2 (see Appendix A1 for a description of FAERS database) for name confusion errors involving Doryx since our previous FAERS search that would be relevant for this review.

Table 2. FAERS Search Strategy	
Search Date	January 22, 2016
Drug Name	Doryx [product name]
Event (MedDRA Terms)	**DMEPA Official Proprietary Name Review Search Terms Event List:** Product name confusion (PT) Medication error (PT) Intercepted medication error (PT) Drug dispensing error (PT) Intercepted drug dispensing error (PT) Circumstance or information capable of leading to a medication error (PT)
Date Limits	August 11, 2015 to January 22, 2016 (gap search since the FAERS search performed in RCM # 2015-996751)

Our gap search since the previous FAERS Search conducted in OSE Review # 2015-996751 retrieved zero additional cases.

2.2.6 Communication of DMEPA's Analysis at Midpoint of Review

DMEPA communicated our findings to the Division of Anti-Infective Products (DAIP) via e-mail on March 4, 2016. At that time we also requested additional information or

[4] Committee on Drugs, American Academy of Pediatrics. Reappraisal of lytic cocktail/Demerol, Phenergan, and Thorazine (DPT) for the sedation of children. Pediatrics 1995;95:598–602.

concerns that could inform our review. Per e-mail correspondence from the DAIP on March 11, 2016, they stated no additional concerns with the proposed proprietary name, Doryx MPC.

3 CONCLUSIONS

The proposed proprietary name is acceptable.

If you have any questions or need clarifications, please contact Karen Townsend, OSE project manager, at 301-796-5413.

3.1 COMMENTS TO THE APPLICANT

We have completed our review of the proposed proprietary name, Doryx MPC, and have concluded that this name is acceptable.

If any of the proposed product characteristics as stated in your December 24, 2015 submission are altered prior to approval of the marketing application, the name must be resubmitted for review.

4 REFERENCES

1. ***USAN Stems*** *(http://www.ama-assn.org/ama/pub/physician-resources/medical-science/united-states-adopted-names-council/naming-guidelines/approved-stems.page)*

   USAN Stems List contains all the recognized USAN stems.

2. ***Phonetic and Orthographic Computer Analysis (POCA)***

POCA is a system that FDA designed. As part of the name similarity assessment, POCA is used to evaluate proposed names via a phonetic and orthographic algorithm. The proposed proprietary name is converted into its phonemic representation before it runs through the phonetic algorithm. Likewise, an orthographic algorithm exists that operates in a similar fashion. POCA is publicly accessible.

Drugs@FDA

Drugs@FDA is an FDA Web site that contains most of the drug products approved in the United States since 1939. The majority of labels, approval letters, reviews, and other information are available for drug products approved from 1998 to the present. Drugs@FDA contains official information about FDA-approved *brand name* and *generic drugs*; *therapeutic biological products*, *prescription* and *over-the-counter* human drugs; and *discontinued drugs* (see Drugs @ FDA Glossary of Terms, available at http://www.fda.gov/Drugs/InformationOnDrugs/ucm079436.htm#ther_biological).

RxNorm

RxNorm contains the names of prescription and many OTC drugs available in the United States. RxNorm includes generic and branded:

- Clinical drugs – pharmaceutical products given to (or taken by) a patient with therapeutic or diagnostic intent
- Drug packs – packs that contain multiple drugs, or drugs designed to be administered in a specified sequence

Radiopharmaceuticals, contrast media, food, dietary supplements, and medical devices, such as bandages and crutches, are all out of scope for RxNorm (http://www.nlm.nih.gov/research/umls/rxnorm/overview.html#).

Division of Medication Errors Prevention and Analysis proprietary name consultation requests

This is a list of proposed and pending names that is generated by the Division of Medication Error Prevention and Analysis from the Access database/tracking system.

3. ***Electronic Drug Registration and Listing System (eDRLS) database***

The electronic Drug Registration and Listing System (eDRLS) was established to supports the FDA's Center for Drug Evaluation and Research (CDER) goal to establish a common Structured Product Labeling (SPL) repository for all facilities that manufacture regulated drugs. The system is a reliable, up-to-date inventory of FDA-regulated, drugs and establishments that produce drugs and their associated information.

APPENDICES

Appendix A

FDA's Proprietary Name Risk Assessment evaluates proposed proprietary names for misbranding and safety concerns.

1. **Misbranding Assessment**: For prescription drug products, OPDP assesses the name for misbranding concerns. . For over-the-counter (OTC) drug products, the misbranding assessment of the proposed name is conducted by DNDP. OPDP or DNDP evaluates proposed proprietary names to determine if the name is false or misleading, such as by making misrepresentations with respect to safety or efficacy. For example, a fanciful proprietary name may misbrand a product by suggesting that it has some unique effectiveness or composition when it does not (21 CFR 201.10(c)(3)). OPDP or DNDP provides their opinion to DMEPA for consideration in the overall acceptability of the proposed proprietary name.
2. **Safety Assessment**: The safety assessment is conducted by DMEPA, and includes the following:

a. Preliminary Assessment: We consider inclusion of USAN stems or other characteristics that when incorporated into a proprietary name may cause or contribute to medication errors (i.e., dosing interval, dosage form/route of administration, medical or product name abbreviations, names that include or suggest the composition of the drug product, etc.) See prescreening checklist below in Table 2*. DMEPA defines a medication error as any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer. [5]

[5] National Coordinating Council for Medication Error Reporting and Prevention. http://www.nccmerp.org/aboutMedErrors.html. Last accessed 10/11/2007.

***Table 2- Prescreening Checklist for Proposed Proprietary Name**

	Answer the questions in the checklist below. Affirmative answers to any of these questions indicate a potential area of concern that should be carefully evaluated as described in this guidance.
Y/N	**Is the proposed name obviously similar in spelling and pronunciation to other names?**
	Proprietary names should not be similar in spelling or pronunciation to proprietary names, established names, or ingredients of other products.
Y/N	**Are there medical and/or coined abbreviations in the proprietary name?**
	Proprietary names should not incorporate medical abbreviations (e.g., QD, BID, or others commonly used for prescription communication) or coined abbreviations that have no established meaning.
Y/N	**Are there inert or inactive ingredients referenced in the proprietary name?**
	Proprietary names should not incorporate any reference to an inert or inactive ingredient in a way that might create an impression that the ingredient's value is greater than its true functional role in the formulation (21 CFR 201.10(c)(4)).
Y/N	**Does the proprietary name include combinations of active ingredients?**
	Proprietary names of fixed combination drug products should not include or suggest the name of one or more, but not all, of its active ingredients (see 21 CFR 201.6(b)).
Y/N	**Is there a United States Adopted Name (USAN) stem in the proprietary name?**
	Proprietary names should not incorporate a USAN stem in the position that USAN designates for the stem.
Y/N	**Is this proprietary name used for another product that does not share at least one common active ingredient?**
	Drug products that do not contain at least one common active ingredient should not use the same (root) proprietary name.
Y/N	**Is this a proprietary name of a discontinued product?**
	Proprietary names should not use the proprietary name of a discontinued product if that discontinued drug product does not contain the same active ingredients.

b. Phonetic and Orthographic Computer Analysis (POCA): Following the preliminary screening of the proposed proprietary name, DMEPA staff evaluates the proposed name against potentially similar names. In order to identify names with potential similarity to the proposed proprietary name, DMEPA enters the proposed proprietary name in POCA and queries the name against the following drug reference databases, Drugs@fda, CernerRxNorm, and names in the review pipeline using a 50% threshold in POCA. DMEPA reviews the combined orthographic and phonetic matches and group the names into one of the following three categories:

- Highly similar pair: combined match percentage score ≥70%.
- Moderately similar pair: combined match percentage score ≥50% to ≤ 69%.
- Low similarity: combined match percentage score ≤49%.

Using the criteria outlined in the check list (Table 3-5) that corresponds to each of the three categories (highly similar pair, moderately similar pair, and low similarity), DMEPA evaluates the name pairs to determine the acceptability or non-acceptability of a proposed proprietary name. The intent of these checklists is to increase the transparency and predictability of the safety determination of whether a proposed name is vulnerable to confusion from a look-alike or sound-alike perspective. Each bullet below corresponds to the name similarity category cross-references the respective table that addresses criteria that DMEPA uses to determine whether a name presents a safety concern from a look-alike or sound-alike perspective.

- For highly similar names, differences in product characteristics often cannot mitigate the risk of a medication error, including product differences such as strength and dose. Thus, proposed proprietary names that have a combined score of ≥ 70 percent are at risk for a look-alike sound-alike confusion which is an area of concern (See Table 3).
- Moderately similar names with overlapping or similar strengths or doses represent an area for concern for FDA. The dosage and strength information is often located in close proximity to the drug name itself on prescriptions and medication orders, and it can be an important factor that either increases or decreases the potential for confusion between similarly named drug pairs. The ability of other product characteristics to mitigate confusion (e.g., route, frequency, dosage form, etc.) may be limited when the strength or dose overlaps. We review such names further, to determine whether sufficient differences exist to prevent confusion. (See Table 4).
- Names with low similarity that have no overlap or similarity in strength and dose are generally acceptable (See Table 5) unless there are data to suggest that the name might be vulnerable to confusion (e.g., prescription simulation study suggests that the name is likely to be misinterpreted as a marketed product). In these instances, we would reassign a low similarity name to the moderate similarity category and review according to the moderately similar name pair checklist.

c. FDA Prescription Simulation Studies: DMEPA staff also conducts a prescription simulation studies using FDA health care professionals.

Three separate studies are conducted within the Centers of the FDA for the proposed proprietary name to determine the degree of confusion of the proposed proprietary name with marketed U.S. drug names (proprietary and established) due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. The studies employ healthcare professionals (pharmacists, physicians, and nurses), and attempts to simulate the prescription ordering process. The primary Safety Evaluator uses the results to identify orthographic or phonetic vulnerability of the proposed name to be misinterpreted by healthcare practitioners.

In order to evaluate the potential for misinterpretation of the proposed proprietary name in handwriting and verbal communication of the name, inpatient medication orders and/or outpatient prescriptions are written, each consisting of a combination of marketed and unapproved drug products, including the proposed name. These orders are optically scanned and one prescription is delivered to a random sample of participating health professionals via e-mail. In addition, a verbal prescription is recorded on voice mail. The voice mail messages are then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants record their interpretations of the orders which are recorded electronically.

d. Comments from Other Review Disciplines: DMEPA requests the Office of New Drugs (OND) and/or Office of Generic Drugs (OGD), ONDQA or OBP for their comments or concerns with the proposed proprietary name, ask for any clinical issues that may impact the DMEPA review during the initial phase of the name review. Additionally, when applicable, at the same time DMEPA requests concurrence/non-concurrence with OPDP's decision on the name. The primary Safety Evaluator addresses any comments or concerns in the safety evaluator's assessment.

The OND/OGD Regulatory Division is contacted a second time following our analysis of the proposed proprietary name. At this point, DMEPA conveys their decision to accept or reject the name. The OND or OGD Regulatory Division is requested to provide any further information that might inform DMEPA's final decision on the proposed name.

Additionally, other review disciplines opinions such as ONDQA or OBP may be considered depending on the proposed proprietary name.

When provided, DMEPA considers external proprietary name studies conducted by or for the Applicant/Sponsor and incorporates the findings of these studies into the overall risk assessment.

The DMEPA primary reviewer assigned to evaluate the proposed proprietary name is responsible for considering the collective findings, and provides an overall risk assessment of the proposed proprietary name.

Table 3. Highly Similar Name Pair Checklist (i.e., combined Orthographic and Phonetic score is ≥ 70%).

Answer the questions in the checklist below. Affirmative answers to some of these questions suggest that the pattern of orthographic or phonetic differences in the names may render the names less likely to confusion, provided that the pair does not share a common strength or dose.

Orthographic Checklist		Phonetic Checklist	
Y/N	Do the names begin with different first letters? *Note that even when names begin with different first letters, certain letters may be confused with each other when scripted.*	Y/N	Do the names have different number of syllables?
Y/N	Are the lengths of the names dissimilar* when scripted? **FDA considers the length of names different if the names differ by two or more letters.*	Y/N	Do the names have different syllabic stresses?
Y/N	Considering variations in scripting of some letters (such as *z* and *f*), is there a different number or placement of upstroke/downstroke letters present in the names?	Y/N	Do the syllables have different phonologic processes, such vowel reduction, assimilation, or deletion?
Y/N	Is there different number or placement of cross-stroke or dotted letters present in the names?	Y/N	Across a range of dialects, are the names consistently pronounced differently?
Y/N	Do the infixes of the name appear dissimilar when scripted?		
Y/N	Do the suffixes of the names appear dissimilar when scripted?		

Table 4: Moderately Similar Name Pair Checklist (i.e., combined score is ≥50% to ≤69%).

Step 1	Review the DOSAGE AND ADMINISTRATION and HOW SUPPLIED/STORAGE AND HANDLING sections of the prescribing information (or for OTC drugs refer to the Drug Facts label) to determine if strengths and doses of the name pair overlap or are very similar. Different strengths and doses for products whose names are moderately similar may decrease the risk of confusion between the moderately similar name pairs. Name pairs that have overlapping or similar strengths or doses have a higher potential for confusion and should be evaluated further (see Step 2). Because the strength or dose could be used to express an order or prescription for a particular drug product, overlap in one or both of these components would be reason for further evaluation. For single strength products, also consider circumstances where the strength may not be expressed. For any i.e. drug products comprised of more than one active ingredient, consider whether the strength or dose may be expressed using only one of the components. To determine whether the strengths or doses are similar to your proposed product, consider the following list of factors that may increase confusion: • Alternative expressions of dose: 5 mL may be listed in the prescribing information, but the dose may be expressed in metric weight (e.g., 500 mg) or in non-metric units (e.g., 1 tsp, 1 tablet/capsule). Similarly, a strength or dose of 1000 mg may be expressed, in practice, as 1 g, or vice versa. • Trailing or deleting zeros: 10 mg is similar in appearance to 100 mg which may potentiate confusion between a name pair with moderate similarity. • Similar sounding doses: 15 mg is similar in sound to 50 mg
Step 2	Answer the questions in the checklist below. Affirmative answers to some of these questions suggest that the pattern of orthographic or phonetic differences in the names may reduce the likelihood of confusion for moderately similar names **with** overlapping or similar strengths or doses.

	Orthographic Checklist (Y/N to each question)	Phonetic Checklist (Y/N to each question)
	• Do the names begin with different first letters? Note that even when names begin with different first letters, certain letters may be confused with each other when scripted. • Are the lengths of the names dissimilar* when scripted? *FDA considers the length of names different if the names differ by two or more letters. • Considering variations in scripting of some letters (such as *z* and *f*), is there a different number or placement of upstroke/downstroke letters present in the names? • Is there different number or placement of cross-stroke or dotted letters present in the names? • Do the infixes of the name appear dissimilar when scripted? • Do the suffixes of the names appear dissimilar when scripted?	• Do the names have different number of syllables? • Do the names have different syllabic stresses? • Do the syllables have different phonologic processes, such vowel reduction, assimilation, or deletion? • Across a range of dialects, are the names consistently pronounced differently?

Table 5: Low Similarity Name Pair Checklist (i.e., combined score is ≤49%).

In most circumstances, these names are viewed as sufficiently different to minimize confusion. Exceptions to this would occur in circumstances where, for example, there are data that suggest a name with low similarity is nonetheless misinterpreted as a marketed product name in a prescription simulation study. In such instances, FDA would reassign a low similarity name to the moderate similarity category and review according to the moderately similar name pair checklist.

Appendix A1: Description of FAERS

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's postmarket safety surveillance program for drug and therapeutic biologic products. The informatic structure of the FAERS database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. FDA's Office of Surveillance and Epidemiology codes adverse events and medication errors to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. Product names are coded using the FAERS Product Dictionary. More information about FAERS can be found at: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm.

Appendix B: Prescription Simulation Samples and Results

Figure 1. Doryx MPC Study (Conducted on January 20, 2016)

Handwritten Requisition Medication Order	Verbal Prescription
Medication Order: Doryx MPC 120mg Take one tablet po daily #30	Doryx MPC 120 mg Take one tablet by mouth daily. Dispense #30
Outpatient Prescription: Doryx MPC 120mg po q12hr x 1 day then 120mg qd	

FDA Prescription Simulation Responses (Aggregate 1 Rx Studies Report)

239 People Received Study
77 People Responded

Study Name: Doryx MPC

Total	29	22	26	
INTERPRETATION	OUTPATIENT	VOICE	INPATIENT	TOTAL
DORAX MTC	0	1	0	1
DOREX MPC	0	5	0	5
DOREX MTC	0	2	0	2
DORIX FTC	0	1	0	1
DORIX MPC	0	4	0	4
DORX MPC	0	0	1	1
DORYN MPC	1	0	0	1
DORYX MCT	0	1	0	1
DORYX MPC	28	8	25	61

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

/s/

DEBORAH E MYERS
03/14/2016

BRENDA V BORDERS-HEMPHILL
03/14/2016

PROPRIETARY NAME REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	October 13, 2015
Application Type and Number:	NDA 050795
Product Name and Strength:	Doryx (b)(4) (Doxycycline hyclate) Delayed Release Tablets 60 mg, 120 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Mayne Pharma
Panorama #:	2015-996751
DMEPA Primary Reviewer:	Jacqueline Sheppard, PharmD
DMEPA Team Leader:	Vicky Borders-Hemphill, PharmD
DMEPA Associate Director:	Lubna Merchant, PharmD, MS

Contents

1 INTRODUCTION

This review evaluates the proposed proprietary name, Doryx [(b)(4)] from a safety and misbranding perspective. The sources and methods used to evaluate the proposed name are outlined in the reference section and Appendix A respectively. The Applicant did not submit an external name study for this proposed proprietary name.

1.1 PRODUCT INFORMATION

The following product information is provided in the July 15, 2015 proprietary name submission.

Table 1. Relevant Product Information for Doryx [(b)(4)] and Doryx

Product Name	**Doryx [(b)(4)]**	**Doryx**
Initial Approval Date	N/A	July 21, 2004 (tablet)
Active Ingredient	Doxycycline Hyclate	Doxycyline Hyclate
Proposed Pronunciation	dor -x [(b)(4)]	dor -x
Indication	treatment or prophylaxis of the following conditions or diseases: rickettsial infections, sexually transmitted infections, respiratory tract infections, specific bacterial infections, ophthalmic infections, anthrax, adjunctive therapy for acute intestinal amebiasis and severe acne, and prophylaxis of malaria	
Route of Administration	Oral	Oral
Dosage Form	Delayed Release Tablet	Delayed Release Tablet
Strengths	60 mg, 120 mg	50 mg, 75 mg, 80 mg, 100 mg, 150 mg, 200 mg

Table 1. Relevant Product Information for Doryx [(b)(4)] and Doryx		
Product Name	**Doryx** [(b)(4)]	**Doryx**
Dose and Frequency	Adults: 240 mg on the first day of treatment (administered 120 mg every 12 hours) followed by a maintenance dose of 120 mg daily. The maintenance dose may be administered as a single dose or as 60 mg every 12 hours. In the management of more severe infections (particularly chronic infections of the urinary tract), 120 mg every 12 hours is recommended Pediatric: The recommended dosage schedule for children weighing 45 kg or less is 5.3 mg/kg of body weight divided into two doses on the first day of treatment, followed by 2.6 mg/kg of body weight given as a single daily dose or divided into two doses on subsequent days. For more severe infections up to [(b)(4)] mg/kg of body weight may be used. For children over 45 kg, the usual adult dose should be used	Adults: 200 mg on the first day of treatment (administered 100 mg every 12 hours) followed by a maintenance dose of 100 mg daily. The maintenance dose may be administered as a single dose or as 50 mg every 12 hours. In the management of more severe infections (particularly chronic infections of the urinary tract), 100 mg every 12 hours is recommended Pediatric: The recommended dosage schedule for children weighing 45 kg or less is 4.4 mg/kg of body weight divided into two doses on the first day of treatment, followed by 2.2 mg/kg of body weight given as a single daily dose or divided into two doses on subsequent days. For more severe infections up to 4.4 mg/kg of body weight may be used. For children over 45 kg, the usual adult dose should be used
How Supplied	60 and 120 count bottles	60 and 120 count bottles
Storage	Controlled Room Temperature	Controlled Room Temperature

2 RESULTS

The following sections provide information obtained and considered in the overall evaluation of the proposed proprietary name.

2.1 MISBRANDING ASSESSMENT

The Office of Prescription Drug Promotion (OPDP) determined that the proposed name would not misbrand the proposed product. DMEPA and the Division of Anti-Infective Products (DAIP) concurred with the findings of OPDP's assessment of the proposed name.

2.2 SAFETY ASSESSMENT

The following aspects were considered in the safety evaluation of the name.

2.2.1 United States Adopted Names (USAN) Search

There is no USAN stem present in the proprietary name[1].

2.2.2 Components of the Proposed Proprietary Name

The Applicant did not provide a derivation or intended meaning for the proposed name, Doryx (b)(4) in their submission. The proprietary name, Doryx (b)(4) is comprised of a two words, the root name 'Doryx' and the modifier (b)(4)

The Applicant proposes using the name Doryx as the root name which is currently used for a marketed delayed release doxycycline hyclate product that has the same indications, same active ingredient but with a modified formulation, same frequency of administration, and similar doses. The strength presentations differ (50 mg, 75mg, 80 mg, 100 mg, 150 mg, and 200 mg vs. 60 mg and 120mg) between the two formulations. The Applicant indicated in their submission that the proposed modifier, (b)(4) is intended to mean (b)(4) as the formulation (b)(4) (b)(4) We assess the modifier in Section 2.2.2.2.

2.2.2.1 Safety Assessment of the root name, Doryx

We find using the use of the same root name, Doryx, for this product acceptable. This new formulation will have the same indications, same active ingredient, same frequency of administration, but with non-overlapping strength presentations that those of the current formulations of Doryx. Given the applicant's proposal to use a modifier, we evaluated the potential risk of confusion within the Doryx product line. Our search of the FAERS database did not identify any confusion within the existing Doryx product line. We note that by using unique strengths for the modified formulation, the current product line and modified formulation are further differentiated within the adult dosing range. While the two formulations cannot be interchanged, we can safely address these changes with the use of an appropriate modifier and labeling interventions.

2.2.2.2 Safety Assessment of the Modifier

The Applicant proposes the use of a modifier, (b)(4), which is not a standard modifier, nor does it have an established meaning. The modifier is intended to differentiate the proposed product from the original delayed release formulation and to convey a modified dosage formulation. The Applicant indicates that the modifier (b)(4) represents (b)(4) as the formulation (b)(4) (b)(4)

[1]USAN stem search conducted on August 11, 2015.

[redacted] The use of the term [redacted] does not adequately describe the [redacted] Mayne Pharmaceuticals did not provide any data to support that healthcare professionals and consumers understand the meaning of the term [redacted] and not confuse it with [redacted] DAIP's clinical team expressed the concern that [redacted] could be misinterpreted as [redacted] This was demonstrated in the FDA Prescription Simulation Study wherein a participant in the written study misinterpreted "Doryx [redacted] as "Doryx [redacted] The modifier [redacted] has been [redacted] as a modifier to convey a modified dosage formulation for [redacted]

We note that Mayne Pharmaceuticals provided [redacted] data to support their claim that the proposed product's [redacted] Per the Biopharmaceutics reviewer in an email dated September 18, 2015, they state that '[redacted] Thus, the proposed modifier and its intended meaning of [redacted] FDA generally encourages the use of an existing modifier with an established meaning in order to decrease the risk that end users could misinterpret the modifiers intended meaning leading to medication errors[3]. However, there are no modifiers currently in use that will represent the proposed product characteristic differences between Doryx and Doryx [redacted] We are concerned that the proposed modifier '[redacted] does not clearly identify the modified dosage formulation and its expected properties and the applicant has not provided adequate data to support the claim that the formulation provides [redacted]

We conveyed the concerns related to the modifier to Mayne Pharmaceuticals during a teleconference discussion on September 25, 2015. In a response dated October 7, 2015, Mayne referenced the [redacted] modifier, however as noted above we do not consider the [redacted] is adequate.

2.2.3 Medication Error Data Selection of Cases

We searched the FDA Adverse Event Reporting System (FAERS) database using the strategy listed in Table 2 (see Appendix A1 for a description of FAERS database) for name confusion errors involving Doryx which would be relevant for this review.

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3 [1]Food and Drug Administration. *Guidance for Industry: Best Practices in Developing Proprietary Names for Drugs (Draft Guidance)*, May 2014. Available at

http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm399897.pdf

Table 2. FAERS Search Strategy	
Date	**August 11, 2015**
Drug Name(Product Name)	**Doryx** [product name]
MedDRA Event Search	**DMEPA Official Proprietary Name Review Search Terms Event List:** Product name confusion (PT) Medication error (PT) Intercepted medication error (PT) Drug dispensing error (PT) Intercepted drug dispensing error (PT) Circumstance or information capable of leading to a medication error (PT)
Time/Date Limits	No limits

Each report was reviewed for relevancy and duplication. Duplicates were merged into a single case. The NCC MERP Taxonomy of Medication Errors was used to code the case outcome and error root causes when provided by the reporter.

Our search retrieved two cases, but after further evaluation, we did not identify any medication error cases that were relevant for this review.

2.2.4 FDA Name Simulation Studies

77 practitioners participated in DMEPA's prescription studies. The responses did not sound or look similar to any currently marketed products or any products in the pipeline. However, two responses overlapped with a currently marketed product. Two participants in the written study misinterpreted Doryx (b)(4) as Doryx from two different samples. We note that one participant in the written study misinterpreted Doryx (b)(4) as Doryx (b)(4) and we assess this modifier confusion in Section 2.2.2.1. Appendix B contains the results from the verbal and written prescription studies.

2.2.5 Comments from Other Review Disciplines at Initial Review

In an email dated August 14, 2015, the Division of Anti-Infective Products (DAIP) objected to the name on two issues. The first reason was "we don't think this is an (b)(4) formulation, as the (b)(4)." Secondly, "the dose of Doryx (b)(4) is 120 mg for bioequivalence to 100 mg of existing formulations of Doryx. This will require different dosing and administration instructions in the label….We do think there needs to be some means to distinguish between this new formulation of doxycycline and the already marketed Doryx delayed release tablets…don't believe the (b)(4) designation is sufficient to distinguish these 120 mg and 60 mg tablets from the other Doryx tablets." These issues are evaluated in section 2.2.2.1 and 2.2.2.2.

3 CONCLUSIONS

The proposed proprietary name is not acceptable from a safety perspective. We are concerned with the use of the modifier (b)(4) Therefore, the decision to deny the name will be communicated to the Sponsor via letter (See ***Section 3.1).***

If you have further questions or need clarifications, please contact Karen Townsend, OSE project manager, at 301-796-5413.

3.1 COMMENTS TO THE APPLICANT

We have completed our review of the proposed proprietary name, Doryx (b)(4) and have concluded that this name is unacceptable for the following reasons:

You propose the use of a modifier, (b)(4), with the root name Doryx, for this formulation. We note that (b)(4) is not a standard modifier, nor does it have an established meaning. You indicate that the modifier (b)(4) is intended to convey (b)(4) as the formulation (b)(4) (b)(4) (b)(4). However, you did not provide any data to support that healthcare practitioners would understand the meaning of the term (b)(4) and not confuse it with another commonly used modifier.

Additionally, we are concerned that (b)(4) could be misinterpreted as (b)(4) (b)(4) This was demonstrated in the FDA Prescription Simulation Study wherein a participant in the written study misinterpreted "Doryx (b)(4) as "Doryx (b)(4)." The modifier (b)(4) has been commonly used as a modifier to convey ar (b)(4) (b)(4)

Furthermore, you provided (b)(4) data in an attempt to support your claim (b)(4) that the proposed product's (b)(4) not been established for this product. The (b)(4) data do not correlate with the (b)(4) The (b)(4) claim is not justified by using (b)(4) data only. The proposed modifier (b)(4) and its intended meaning of (b)(4) (b)(4) is not supported by the overall data you submitted.

Reference ID: 3832639
Reference ID: 3935555

REFERENCES

1. ***USAN Stems (http://www.ama-assn.org/ama/pub/physician-resources/medical-science/united-states-adopted-names-council/naming-guidelines/approved-stems.page)***

   USAN Stems List contains all the recognized USAN stems.

2. ***Phonetic and Orthographic Computer Analysis (POCA)***

POCA is a system that FDA designed. As part of the name similarity assessment, POCA is used to evaluate proposed names via a phonetic and orthographic algorithm. The proposed proprietary name is converted into its phonemic representation before it runs through the phonetic algorithm. Likewise, an orthographic algorithm exists that operates in a similar fashion. POCA is publicly accessible.

Drugs@FDA

Drugs@FDA is an FDA Web site that contains most of the drug products approved in the United States since 1939. The majority of labels, approval letters, reviews, and other information are available for drug products approved from 1998 to the present. Drugs@FDA contains official information about FDA-approved *brand name* and *generic drugs*; *therapeutic biological products*, *prescription* and *over-the-counter* human drugs; and *discontinued drugs* (see Drugs @ FDA Glossary of Terms, available at http://www.fda.gov/Drugs/InformationOnDrugs/ucm079436.htm#ther_biological).

RxNorm

RxNorm contains the names of prescription and many OTC drugs available in the United States. RxNorm includes generic and branded:

- Clinical drugs – pharmaceutical products given to (or taken by) a patient with therapeutic or diagnostic intent
- Drug packs – packs that contain multiple drugs, or drugs designed to be administered in a specified sequence

Radiopharmaceuticals, contrast media, food, dietary supplements, and medical devices, such as bandages and crutches, are all out of scope for RxNorm (http://www.nlm.nih.gov/research/umls/rxnorm/overview.html#).

Division of Medication Errors Prevention and Analysis proprietary name consultation requests

This is a list of proposed and pending names that is generated by the Division of Medication Error Prevention and Analysis from the Access database/tracking system.

APPENDICES

Appendix A

FDA's Proprietary Name Risk Assessment evaluates proposed proprietary names for misbranding and safety concerns.

1. **Misbranding Assessment**: For prescription drug products, OPDP assesses the name for misbranding concerns. . For over-the-counter (OTC) drug products, the misbranding assessment of the proposed name is conducted by DNDP. OPDP or DNDP evaluates proposed proprietary names to determine if the name is false or misleading, such as by making misrepresentations with respect to safety or efficacy. For example, a fanciful proprietary name may misbrand a product by suggesting that it has some unique effectiveness or composition when it does not (21 CFR 201.10(c)(3)). OPDP or DNDP provides their opinion to DMEPA for consideration in the overall acceptability of the proposed proprietary name.
2. **Safety Assessment**: The safety assessment is conducted by DMEPA, and includes the following:

a. Preliminary Assessment: We consider inclusion of USAN stems or other characteristics that when incorporated into a proprietary name may cause or contribute to medication errors (i.e., dosing interval, dosage form/route of administration, medical or product name abbreviations, names that include or suggest the composition of the drug product, etc.) See prescreening checklist below in Table 2*. DMEPA defines a medication error as any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer. [4]

[4] National Coordinating Council for Medication Error Reporting and Prevention. http://www.nccmerp.org/aboutMedErrors.html. Last accessed 10/11/2007.

***Table 2- Prescreening Checklist for Proposed Proprietary Name**

	Answer the questions in the checklist below. Affirmative answers to any of these questions indicate a potential area of concern that should be carefully evaluated as described in this guidance.
Y/N	**Is the proposed name obviously similar in spelling and pronunciation to other names?**
	Proprietary names should not be similar in spelling or pronunciation to proprietary names, established names, or ingredients of other products.
Y/N	**Are there medical and/or coined abbreviations in the proprietary name?**
	Proprietary names should not incorporate medical abbreviations (e.g., QD, BID, or others commonly used for prescription communication) or coined abbreviations that have no established meaning.
Y/N	**Are there inert or inactive ingredients referenced in the proprietary name?**
	Proprietary names should not incorporate any reference to an inert or inactive ingredient in a way that might create an impression that the ingredient's value is greater than its true functional role in the formulation (21 CFR 201.10(c)(4)).
Y/N	**Does the proprietary name include combinations of active ingredients?**
	Proprietary names of fixed combination drug products should not include or suggest the name of one or more, but not all, of its active ingredients (see 21 CFR 201.6(b)).
Y/N	**Is there a United States Adopted Name (USAN) stem in the proprietary name?**
	Proprietary names should not incorporate a USAN stem in the position that USAN designates for the stem.
Y/N	**Is this proprietary name used for another product that does not share at least one common active ingredient?**
	Drug products that do not contain at least one common active ingredient should not use the same (root) proprietary name.
Y/N	**Is this a proprietary name of a discontinued product?**
	Proprietary names should not use the proprietary name of a discontinued product if that discontinued drug product does not contain the same active ingredients.

b. Phonetic and Orthographic Computer Analysis (POCA): Following the preliminary screening of the proposed proprietary name, DMEPA staff evaluates the proposed name against potentially similar names. In order to identify names with potential similarity to the proposed proprietary name, DMEPA enters the proposed proprietary name in POCA and queries the name against the following drug reference databases, Drugs@fda, CernerRxNorm, and names in the review pipeline using a 50% threshold in POCA. DMEPA reviews the combined orthographic and phonetic matches and group the names into one of the following three categories:

- Highly similar pair: combined match percentage score ≥70%.
- Moderately similar pair: combined match percentage score ≥50% to ≤ 69%.
- Low similarity: combined match percentage score ≤49%.

Using the criteria outlined in the check list (Table 3-5) that corresponds to each of the three categories (highly similar pair, moderately similar pair, and low similarity), DMEPA evaluates the name pairs to determine the acceptability or non-acceptability of a proposed proprietary name. The intent of these checklists is to increase the transparency and predictability of the safety determination of whether a proposed name is vulnerable to confusion from a look-alike or sound-alike perspective. Each bullet below corresponds to the name similarity category cross-references the respective table that addresses criteria that DMEPA uses to determine whether a name presents a safety concern from a look-alike or sound-alike perspective.

- For highly similar names, differences in product characteristics often cannot mitigate the risk of a medication error, including product differences such as strength and dose. Thus, proposed proprietary names that have a combined score of ≥ 70 percent are at risk for a look-alike sound-alike confusion which is an area of concern (See Table 3).
- Moderately similar names with overlapping or similar strengths or doses represent an area for concern for FDA. The dosage and strength information is often located in close proximity to the drug name itself on prescriptions and medication orders, and it can be an important factor that either increases or decreases the potential for confusion between similarly named drug pairs. The ability of other product characteristics to mitigate confusion (e.g., route, frequency, dosage form, etc.) may be limited when the strength or dose overlaps. We review such names further, to determine whether sufficient differences exist to prevent confusion. (See Table 4).
- Names with low similarity that have no overlap or similarity in strength and dose are generally acceptable (See Table 5) unless there are data to suggest that the name might be vulnerable to confusion (e.g., prescription simulation study suggests that the name is likely to be misinterpreted as a marketed product). In these instances, we would reassign a low similarity name to the moderate similarity category and review according to the moderately similar name pair checklist.

c. FDA Prescription Simulation Studies: DMEPA staff also conducts a prescription simulation studies using FDA health care professionals.

   Three separate studies are conducted within the Centers of the FDA for the proposed proprietary name to determine the degree of confusion of the proposed proprietary name with marketed U.S. drug names (proprietary and established) due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. The studies employ healthcare professionals (pharmacists, physicians, and nurses), and attempts to simulate the prescription ordering process. The primary Safety Evaluator uses the results to identify orthographic or phonetic vulnerability of the proposed name to be misinterpreted by healthcare practitioners.

   In order to evaluate the potential for misinterpretation of the proposed proprietary name in handwriting and verbal communication of the name, inpatient medication orders and/or outpatient prescriptions are written, each consisting of a combination of marketed and unapproved drug products, including the proposed name. These orders are optically scanned and one prescription is delivered to a random sample of participating health professionals via e-mail. In addition, a verbal prescription is recorded on voice mail. The voice mail messages are then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants record their interpretations of the orders which are recorded electronically.

d. Comments from Other Review Disciplines: DMEPA requests the Office of New Drugs (OND) and/or Office of Generic Drugs (OGD), ONDQA or OBP for their comments or concerns with the proposed proprietary name, ask for any clinical issues that may impact the DMEPA review during the initial phase of the name review. Additionally, when applicable, at the same time DMEPA requests concurrence/non-concurrence with OPDP's decision on the name. The primary Safety Evaluator addresses any comments or concerns in the safety evaluator's assessment.

   The OND/OGD Regulatory Division is contacted a second time following our analysis of the proposed proprietary name. At this point, DMEPA conveys their decision to accept or reject the name. The OND or OGD Regulatory Division is requested to provide any further information that might inform DMEPA's final decision on the proposed name.

   Additionally, other review disciplines opinions such as ONDQA or OBP may be considered depending on the proposed proprietary name.

When provided, DMEPA considers external proprietary name studies conducted by or for the Applicant/Sponsor and incorporates the findings of these studies into the overall risk assessment.

The DMEPA primary reviewer assigned to evaluate the proposed proprietary name is responsible for considering the collective findings, and provides an overall risk assessment of the proposed proprietary name.

Appendix A1: Description of FAERS

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's postmarket safety surveillance program for drug and therapeutic biologic products. The informatic structure of the FAERS database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. FDA's Office of Surveillance and Epidemiology codes adverse events and medication errors to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. Product names are coded using the FAERS Product Dictionary. More information about FAERS can be found at: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm.

Appendix B: Prescription Simulation Samples and Results

Figure 1. Doryx [(b)(4)] Study (Conducted on July 31, 2015)

Handwritten Requisition Medication Order	Verbal Prescription
Medication Order: Doryx [(b)(4)] 100mg po daily Outpatient Prescription: Doryx [(b)(4)] 120mg 1 tab BID #14	Doryx [(b)(4)] 120 mg Take one tablet twice daily #14

FDA Prescription Simulation Responses (Aggregate 1 Rx Studies Report)

Study Name: Doryx [(b)(4)]
As of Date 8/11/2015

244 People Received Study
77 People Responded

Study Name: Doryx [(b)(4)]

Total	25	22	30	
INTERPRETATION	OUTPATIENT	VOICE	INPATIENT	TOTAL
DIRYX [(b)(4)]	0	0	1	1
DORAX	0	1	0	1
DOREX	0	5	0	5
DORYX	1	0	1	2
DORYX [(b)(4)]	23	4	26	53
DORYX [(b)(4)] 120 MG	1	0	0	1
DORYX [(b)(4)]	0	0	1	1
DOYX [(b)(4)]	0	0	1	1
DUREX	0	11	0	11
DURYX	0	1	0	1

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

/s/

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