

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

50-807

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS



1.3 ADMINISTRATIVE DOCUMENTS

a. Administrative Documents

Patent Information

Mayne Pharma (USA) Inc. is not submitting information on any patent claims for Epirubicin Hydrochloride for Injection, the subject of this application.

Mayne Pharma (USA) Inc. acknowledges patents US 5,977,082 and US 6,107,285 for the Reference Listed Drug, Ellence® (Epirubicin Hydrochloride Injection) 2mg/mL, sponsored by Pfizer, Inc. (previously Pharmacia and Upjohn), approved via NDA 50778 on September 15, 1999.

Mayne also notes that NDA 50778 is subject to the exemption provisions contained in section 125(d)(2) of Title I of the FDA Modernization Act of 1997. Therefore, the patents listed above are not listed on the Electronic Orange Book of Approved Drug Products with Therapeutic Equivalents, current through June 20, 2005 (see Attachment 1.3a).

Paragraph I Certification

In accordance with the Federal Food Drug & Cosmetic Act, as amended September 24, 1984, Patent Certification is hereby provided for our 505(b)(2) application for Epirubicin Hydrochloride Injection.

Mayne hereby certifies that in its opinion and to the best of its knowledge, there are no US patents listed in the Electronic Orange Book of Approved Drug Products with Therapeutic Equivalents.

This certification is made in accordance with Section 505(j)(2)(A)(vii)(II) of Title 1 of the Federal Food, Drug and Cosmetic Act, as amended September 24, 1984 and pursuant to 21 CFR 314.50(i)(i)(1).



Steve Richardson
Director, Regulatory and Medical Affairs
Mayne Pharma (USA) Inc.



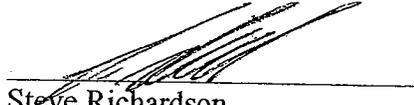
Date



1.3. **ADMINISTRATIVE DOCUMENTS**
a. Administrative Documents
Exclusivity Statement

Mayne Pharma (USA) Inc. certifies that, according to the Electronic Orange book, *Approved Drug Products and their Therapeutic Equivalents*, the Reference Listed Drug, Ellence® (Epirubicin Hydrochloride Injection), approved via NDA 50778, is entitled to a period of exclusivity under 505(j)(4)(D)(iii) of the Federal Food, Drug and Cosmetic Act (the Act) which expires September 15, 2006 (Exclusivity Code: ODE). (See attachment A1.3a.)

Mayne Pharma (USA) Inc. hereby confirms that we are not seeking approval of the enclosed application prior to the expiration of the noted exclusivity period.



Steve Richardson
Director, Regulatory and Medical Affairs
Mayne Pharma (USA) Inc.

7/15/05
Date

EXCLUSIVITY SUMMARY

NDA # 50-807

SUPPL #

HFD # 150 DDOP

Trade Name na

Generic Name epirubicin hydrochloride for injection

Applicant Name Mayne Pharma (USA) Inc.

Approval Date, If Known

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505b2

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 50-778

Ellence (epirubicin hydrochloride injection)

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)

IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of

summary for that investigation.

YES NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new");

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1
IND # YES ! NO
! Explain:

Investigation #2
IND # YES ! NO
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES

Explain:

!

!

! NO

! Explain:

Investigation #2

YES

Explain:

!

!

! NO

! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES

NO

If yes, explain:

Name of person completing form: Paul Zimmerman

Title: Project Manager

Date: 4-21-06

Name of Office/Division Director signing form:

Title: *Acting Dep. Dir.*

Ann Farrell

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA #: 50-807 Supplement Type (e.g. SE5): _____ Supplement Number: _____

Stamp Date: 7-19-2005 Action Date: 8-19-06

HFD 150 Trade and generic names/dosage form: epirubicin hydrochloride for injection, 50mg, 200mg vial

Applicant: Mayne Pharma (USA) Inc. Therapeutic Class: S

Indication(s) previously approved: NA

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: as a component of adjuvant therapy in patients with axillary node tumor involvement following resection of primary breast cancer

Is there a full waiver for this indication (check one)?

- Yes: Please proceed to Section A.
- No: Please check all that apply: Partial Waiver Deferred Completed
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Other: _____

Formatted: Bullets and Numbering

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____	kg _____	mo. _____	yr. _____	Tanner Stage _____
Max _____	kg _____	mo. _____	yr. _____	Tanner Stage _____

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed

Other: _____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed

Other: _____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

cc: NDA 50-807
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 12-22-03)

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: _____

Is there a full waiver for this indication (check one)?

- Yes: Please proceed to Section A.
- No: Please check all that apply: ___ Partial Waiver ___ Deferred ___ Completed
 NOTE: More than one may apply
 Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____	kg _____	mo. _____	yr. _____	Tanner Stage _____
Max _____	kg _____	mo. _____	yr. _____	Tanner Stage _____

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Comments:

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

cc: NDA #~~XXXX~~
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 10-14-03)



1.3 ADMINISTRATIVE DOCUMENTS
a. Administrative Documents
Debarment Certification

Following is a certification from Mayne Pharma which confirms our compliance with section 306(k) of the Federal Food, Drug and Cosmetic Act, as amended, 21 United States Code §336(k); 106 Stat. 158: Pub. L 102-182 (May 13, 1992).

**CERTIFICATION PURSUANT TO SECTION 306(k) OF THE
FEDERAL FOOD, DRUG, AND COSMETIC ACT, AS AMENDED:
PUBLIC LAW 102-282, MAY 13, 1992**

Mayne Pharma (USA) Inc. hereby certifies that:

1. We did not, and will not, use in any capacity the services of any person debarred under subsection (a) or (b) of this section of the Act in connection with this application.
2. That neither the applicant nor any affiliated person responsible for the development or submission of the application have been convicted within the past five (5) years of the offenses described in subsection (a) or (b) of this section of the Act.

Stuart Hinchey
President - Americas
Mayne Pharma (USA) Inc.

6.27.05

Date

**APPEARS THIS WAY
ON ORIGINAL**



1.3

ADMINISTRATIVE DOCUMENTS

a. Administrative Documents

Financial Disclosure

Mayne Pharma (USA) Inc., in our enclosed 505(b)(2) application, has referenced NDA 50778 Ellence® (Epirubicin Hydrochloride Injection) for clinical studies relating to the safety and efficacy of our proposed drug product, Epirubicin Hydrochloride for Injection.

Mayne has not performed clinical studies in support of the enclosed application, or used the services of any clinical investigators. Therefore, there is no financial information to disclose in this section.

**APPEARS THIS WAY
ON ORIGINAL**

Acting Deputy Division Director Summary Review of NDA 50-807
Drug: Epirubicin Hydrochloride for Injection
Applicant: Mayne Pharma, Inc.
Date: July 26, 2006

This is a 505(b)(2) application for Epirubicin Hydrochloride for Injection. This application is for the approved indication of the reference drug, ELLENCE Injection (epirubicin hydrochloride-aqueous solution), as a component of adjuvant therapy in patients with evidence of axillary node tumor involvement following resection of primary breast cancer. Mayne Pharmaceutical proposes that Epirubicin Hydrochloride for Injection be packaged as 50 mg and 200 mg lyophilized powder formulations.

The NDA was originally submitted on July 15, 2005. The review time clock was extended due to submission of a Chemistry, Manufacturing and Controls major amendment on April 28, 2006. The revised PDUFA goal date is August 19, 2006.

Medical Review

The Medical Officer's Review by Drs. Cortazar and Johnson recommended approval.

Clinical Pharmacology Review

A Clinical Pharmacology and Biopharmaceutics Review was completed by Angela Men, Ph.D., and Brian Booth, Ph.D. on March 20, 2006. The change in formulation was found acceptable to the Office of Clinical Pharmacology and Biopharmaceutics.

Chemistry Manufacturing and Control (CMC) Review

The Chemistry Review by Xiao-Hong Chen, Ph.D. and Ravi Harapanhalli, Ph.D. was completed on July 25, 2006.

The review stated that "From a CMC perspective, this application is recommended for approval. The applicant has satisfactorily addressed all CMC deficiencies. The DMF — as amended on June 8, 2006, has been reviewed and found to be adequate. The Office of Compliance has provided an overall "acceptable" recommendation for this application. We recommend that the following comment regarding shelf life be included in the approval letter: An expiration-dating period of 18 months for the drug product is granted based on stability data provided."

Microbiology Review

The Microbiology Review by John Metcalfe, Ph.D. and Bryan Riley, Ph.D. was completed on June 26, 2006. The submission was found to be acceptable and adequate for approval.

Pharmacology/Toxicology Review

The Microbiology Review by Haleh Saber-Mahloogi, Ph.D. and David Morse, Ph.D. was completed on April 19, 2006. The submission was found to be acceptable and adequate for approval.

Division of Medication Errors and Technical Support (DMETS) Consultation

The DMETS consultation dated July 15, 2005 made recommendations to decrease the potential for medication errors. They recommended

- 1) Use of contrasting colors or boxing to better distinguish better distinguish the 50 mg and 200mg strengths
- 2) Revise text to read "Single-Dose Vial. Discard Unused Portion."
- 3) Include a usual dosage statement as stated in 21 CFR 201.55
- 4) Revise the container label and carton labeling to include a comment about reconstitution and increase the prominence of the route of administration

During the review cycle, the sponsor submitted new labeling in response to a suggestion from Office of Generic Drugs (OGD) that Tall man font could be used to distinguish this product from doxorubicin and other cytotoxic agents ending in "rubicin". DMETS did not agree and wanted use of the Tall man font reserved for special situations. After further discussion, CMC, DMETS, and OGD all jointly agreed that for this application Tall man font should not be used. This information was communicated to the company who revised their labeling and removed Tall man font. All issues regarding labeling are resolved at this time.

Conclusion

I concur with the review teams that the application should be approved for the following indication "as a component of adjuvant therapy in patients with evidence of axillary node tumor involvement following resection of primary breast cancer."

**APPEARS THIS WAY
ON ORIGINAL**

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

/s/

Ann Farrell
8/17/2006 09:11:45 AM
MEDICAL OFFICER

PROJECT MANAGER REVIEW OF LABELING

NDA: 50-807

Drug: Epirubicin hydrochloride for injection

Applicant: Mayne Pharma (USA) Inc.

Submission Dates: July 14, 2006 **Receipt Date:** July 17, 2006

BACKGROUND:

This new NDA 50-807 dated July 15, 2005 was submitted as 505b2, relying on NDA 50-778 for Ellence (epirubicin hydrochloride injection) for non-clinical and clinical studies for safety and effectiveness.

DOCUMENTS REVIEWED:

The approved labeling text from the March 2, 2005 NDA 50-778/S-008 (Ellence) approval letter is compared with the July 14, 2006 labeling text submitted by Mayne.

Listed and proposed 50 mg and 200 mg cartons and containers from the July 14, 2006 submission are compared.

REVIEW:

PACKAGE INSERT

Throughout the labeling ELLENCE Injection (epirubicin hydrochloride injection) is changed to Epirubicin Hydrochloride for Injection.

The Title is changed from Ellence® epirubicin hydrochloride injection to EPIrubicin Hydrochloride for Injection.

In DESCRIPTION, the first paragraph is changed from:

ELLENCE Injection (epirubicin hydrochloride injection) is an anthracycline cytotoxic agent, intended for intravenous administration. ELLENCE is supplied as a sterile, clear, red solution and is available in polypropylene vials containing 50 and 200 mg of epirubicin hydrochloride as a preservative-free, ready-to-use solution. Each milliliter of solution contains 2 mg of epirubicin hydrochloride. Inactive ingredients include sodium chloride, USP, and water for injection, USP. The pH of the solution has been adjusted to 3.0 with hydrochloric acid, NF.

To:

Epirubicin Hydrochloride for Injection is an anthracycline cytotoxic agent, intended for intravenous administration. Epirubicin Hydrochloride for Injection is

supplied as a sterile, orange-red, lyophilized powder in single-dose vials containing 50 mg or 200 mg of epirubicin hydrochloride. Each 50 mg and 200 mg vial contains 250 mg and 1000 mg inactive ingredient, lactose, respectively.

In DOSAGE AND ADMINISTRATION, Preparation of Infusion Solution, the following Reconstitution section has been added.

Prior to use, Epirubicin Hydrochloride for Injection 50 mg and 200 mg vials must be reconstituted with 25 mL and 100 mL, respectively, of Sterile Water for Injection, USP, resulting in a solution concentration of 2 mg/mL with a pH of 4.7 to 5.0. Shake vigorously. It may take up to 4 minutes for epirubicin hydrochloride to completely dissolve. Reconstituted solutions are stable for 24 hours when stored at 2 to 8°C (36 to 46°F) and protected from light, or 25°C (77°F) in normal lighting conditions.

Epirubicin Hydrochloride for Injection can be further diluted with Sterile Water for Injection, USP.

In DOSAGE AND ADMINISTRATION, Preparation of Infusion Solution, "Administration" title is added to the existing approved text and the following sentence is deleted: ELLENCE is provided as a preservative free, ready to use solution.

The HOW SUPPLIED section has changed from:

ELLENCE Injection is available in polypropylene single-use vials containing 2 mg epirubicin hydrochloride per mL as a sterile, preservative-free, ready-to-use solution in the following strengths:

50 mg/25 mL single-use vial NDC 0009-5091-01

200 mg/100 mL single-use vial NDC 0009-5093-01

Store refrigerated between 2°C and 8°C (36°F and 46°F). Do not freeze. Protect from light. Discard unused portion.

Rx only

US Patent No. 5,977,082

Manufactured for: Pharmacia & Upjohn Company, A subsidiary of Pharmacia Corporation, Kalamazoo, MI 49001 USA

By: Pharmacia (Perth) Pty Limited, Bentley WA 6102 Australia

February 2005

To:

Epirubicin Hydrochloride for Injection is available in single-use vials containing 50 mg and 200 mg epirubicin hydrochloride.

50 mg/vial NDC 61703-347-35

200 mg/vial NDC 61703-348-59

Store unopened vials at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]. Protect from light. Discard unused portion. Store upright.

The following is included before the REFERENCES section:

* Septra[®] and Bactrim[®] are registered trademarks of Monarch Pharmaceuticals, Inc. and Mutual Pharmaceutical Company Inc., respectively.

The following is included after the REFERENCES section:

Manufactured by:
Mayne Pharma Limited
Mulgrave, VIC 3170
Australia

Distributed by:
Mayne Pharma (USA) Inc.
Paramus, NJ 07652

Made in Australia

Revision July 2006

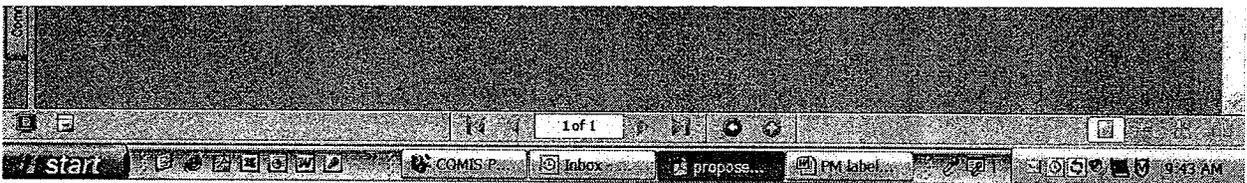
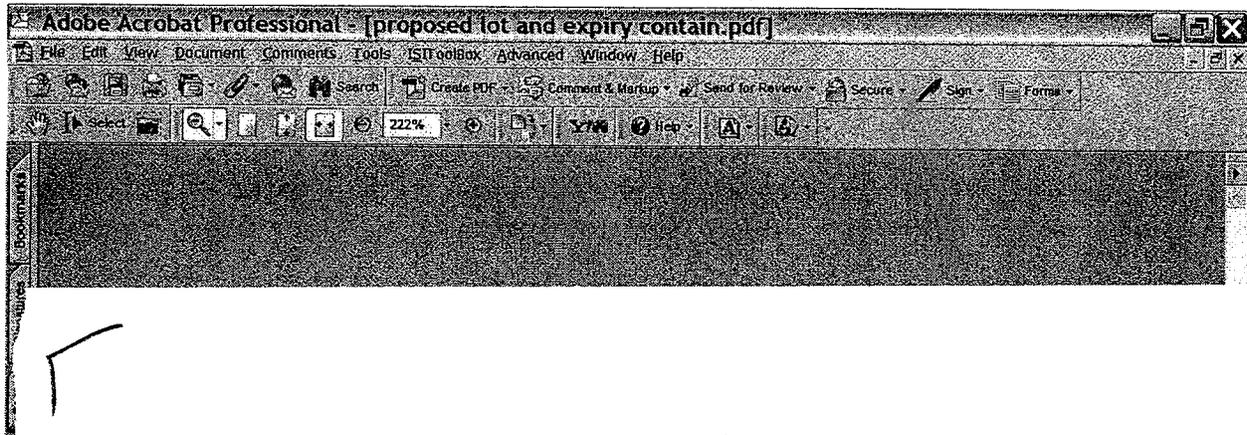
841516

9 Page(s) Withheld

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

 § 552(b)(4) Draft Labeling

 § 552(b)(5) Deliberative Process



CONCLUSION - RECOMMENDED REGULATORY ACTION

Those listed below should comment regarding the proposed package insert. If there are no problems, the NDA labeling should be approved and FPL requested.

Paul Zimmerman, R.Ph., Project Manager/7-19-06

concur-----
Dotti Pease, CPMS/date

concur-----
Xiao Chen, Ph.D., Chemistry Reviewer/date

concur-----

Ravi Harapanhalli, Ph.D., Chemistry Branch Chief/date

concur-----

Angela Men, Ph.D., Biopharmaceutics Reviewer/date

concur-----

Brian Booth, Ph.D., Biopharmaceutics Team Leader/date

concur-----

Haleh Mahloogi, Ph.D., Pharmacology Reviewer/date

concur-----

David Morse, Ph.D., Pharmacology Team Leader/date

concur-----

Patricia Cortazar, MD, Medical Officer/date

concur-----

John Johnson, M.D., Medical Team Leader/date

53 Page(s) Withheld

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

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Zimmerman, Paul F

From: Zimmerman, Paul F
Sent: Wednesday, July 12, 2006 10:22 AM
To: 'Berger, Stephani'
Subject: NDA 50-807 for epirubicin

Stephani,
We have the following additional labeling requests.

uic

In addition, regarding the package insert.

Please add the sentence "It may take up to 4 minutes for epirubicin hydrochloride to completely dissolve." as follows.

Preparation of Infusion Solution

Reconstitution

Prior to use, Epirubicin Hydrochloride for Injection 50 mg and 200 mg vials must be reconstituted with 25 mL and 100 mL, respectively, of Sterile Water for Injection, USP, resulting in a solution concentration of 2 mg/mL with a pH of 4.7 to 5.0. It may take up to 4 minutes for epirubicin hydrochloride to completely dissolve. Reconstituted solutions are stable for 24 hours when stored at 2 to 8°C (36 to 46°F) and protected from light, or 25°C (77°F) in normal lighting conditions.

In HOW SUPPLIED, please make the indicated changes (manufactured by, distributed by) as follows.

HOW SUPPLIED

Epirubicin Hydrochloride for Injection is available in single-use vials containing 50 mg and 200 mg epirubicin hydrochloride.

50 mg/vial NDC 61703-347-35
200 mg/vial NDC 61703-348-59

Store unopened vials at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]. Protect from light. Discard unused portion. Store Upright.

Manufactured by:

.....(Add manufacturer's name and address here)

Distributed by:

.....(If the distributor is different from the manufacturer, add distributor's name and address here)

Thanks,
Paul

**APPEARS THIS WAY
ON ORIGINAL**



NDA 50-807

INFORMATION REQUEST LETTER

Mayne Pharma (USA) Inc.
Attention: Steve Richardson
Director, Regulatory and Medical Affairs
Mack-Cali Centre II
650 From Road, Second Floor
Paramus, NJ 07652

Dear Mr. Richardson,

Please refer to your July 15, 2005 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for (epirubicin hydrochloride for injection) 50mg/vial and 200mg/vial.

We also acknowledge receipt of your amendments dated April 28, and June 16, 2006.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

Provide a revised drug product specification sheet containing the following:

If you have any questions, call Karl Stiller, Regulatory Health Project Manager, at (301) 796-1993.

Sincerely,

Ravi Harapanhalli, Ph.D.
Branch Chief, Branch V
Division of Pre-Marketing Assessment III
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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

/s/

Ravi Harapanhalli
7/5/2006 03:49:40 PM

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 50807

Supplement #

Efficacy Supplement Type SE-

Trade Name: NA

Established Name: epirubicin hydrochloride for injection

Strengths: 50mg, 200mg vial

Applicant: Mayne Pharma (USA) Inc.

Agent for Applicant: Steve Richardson

Date of Application: July 15, 2005

Date of Receipt: July 19, 2005

Date clock started after UN:

Date of Filing Meeting: 8-22-05

Filing Date: 9-17-05

Action Goal Date (optional):

User Fee Goal Date: 8-19-06

Indication(s) requested: as a component of adjuvant therapy in patients with axillary node tumor involvement following resection of primary breast cancer.

Type of Original NDA: (b)(1) (b)(2)

OR

Type of Supplement: (b)(1) (b)(2)

NOTE:

(3) If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application is a (b)(2), complete Appendix B.

(4) If the application is a supplement to an NDA, please indicate whether the NDA is a (b)(1) or a (b)(2) application:

NDA is a (b)(1) application OR NDA is a (b)(2) application

Therapeutic Classification: S

P

Resubmission after withdrawal?

Resubmission after refuse to file?

Chemical Classification: (1,2,3 etc.) 5

Other (orphan, OTC, etc.)

Form 3397 (User Fee Cover Sheet) submitted:

YES NO

User Fee Status:

Paid

Exempt (orphan, government)

Waived (e.g., small business, public health)

NOTE: If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the

Version: 12/15/2004

This is a locked document. If you need to add a comment where there is no field to do so, unlock the document using the following procedure. Click the 'View' tab; drag the cursor down to 'Toolbars'; click on 'Forms.' On the forms toolbar, click the lock/unlock icon (looks like a padlock). This will allow you to insert text outside the provided fields. The form must then be relocked to permit tabbing through the fields.

product described in the application. Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the user fee staff.

- Is there any 5-year or 3-year exclusivity on this active moiety in an approved (b)(1) or (b)(2) application? YES NO
If yes, explain: NDA 50-778 has ODE expiring 9-15-06

- Does another drug have orphan drug exclusivity for the same indication? YES NO

- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? YES NO

If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES NO
If yes, explain:

- If yes, has OC/DMPQ been notified of the submission? YES NO

- Does the submission contain an accurate comprehensive index? YES NO

- Was form 356h included with an authorized signature? YES NO
If foreign applicant, both the applicant and the U.S. agent must sign.

- Submission complete as required under 21 CFR 314.50? YES NO
If no, explain:

- If an electronic NDA, does it follow the Guidance? N/A YES NO
If an electronic NDA, all forms and certifications must be in paper and require a signature.
Which parts of the application were submitted in electronic format? labeling

Additional comments:

- If an electronic NDA in Common Technical Document format, does it follow the CTD guidance? N/A YES NO

- Is it an electronic CTD (eCTD)? N/A YES NO
If an electronic CTD, all forms and certifications must either be in paper and signed or be electronically signed.

Additional comments:

- Patent information submitted on form FDA 3542a? YES NO

- Exclusivity requested? YES, _____ Years NO
NOTE: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.

- Correctly worded Debarment Certification included with authorized signature? YES NO
If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

NOTE: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge"

- Financial Disclosure forms included with authorized signature? YES NO
(Forms 3454 and 3455 must be included and must be signed by the APPLICANT, not an agent.)
NOTE: Financial disclosure is required for bioequivalence studies that are the basis for approval.
- Field Copy Certification (that it is a true copy of the CMC technical section)? Y NO
- PDUFA and Action Goal dates correct in COMIS? YES NO
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.
- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.
- List referenced IND numbers: 69448
- End-of-Phase 2 Meeting(s) Date(s) _____ NO
If yes, distribute minutes before filing meeting.
- Pre-NDA Meeting(s) Date(s) 5-19-04 NO
If yes, distribute minutes before filing meeting.

Project Management

- Was electronic "Content of Labeling" submitted? YES NO
If no, request in 74-day letter.
- All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC?
YES NO
- Risk Management Plan consulted to ODS/IO? N/A YES NO
- Trade name (plus PI and all labels and labeling) consulted to ODS/DMETS? Y NO
- MedGuide and/or PPI (plus PI) consulted to ODS/DSRCS? N/A YES NO
- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted?
N/A YES NO

If Rx-to-OTC Switch application:

- OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/DSRCS? N/A YES NO
- Has DOTCDP been notified of the OTC switch application? YES NO

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff?
YES NO

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES NO
If no, did applicant submit a complete environmental assessment? YES NO
If EA submitted, consulted to Florian Zielinski (HFD-357)? YES NO
- Establishment Evaluation Request (EER) submitted to DMPQ? YES NO
- If a parenteral product, consulted to Microbiology Team (HFD-805)? YES NO

ATTACHMENT

MEMO OF FILING MEETING

DATE: 8-22-05

BACKGROUND: NDA 50-807 is for Epirubicin Hydrochloride for Injection lyophilized, 50mg and 200 mg as a component of adjuvant therapy in patients with axillary node tumor involvement following resection of primary breast cancer. It is a 505(b)(2) relying on NDA 50-778 for Ellence (epirubicin hydrochloride injection) for non-clinical and clinical studies for safety and effectiveness.

(Provide a brief background of the drug, e.g., it is already approved and this NDA is for an extended-release formulation; whether another Division is involved; foreign marketing history; etc.)

ATTENDEES: Ramzi Dagher, Patricia Cortazar, Brian Booth, Nallaperumal Chidambaram, Xiao Chen, Haleh Mahloogi, David Morse

ASSIGNED REVIEWERS (including those not present at filing meeting) :

<u>Discipline</u>	<u>Reviewer</u>
Medical:	Patricia Cortazar
Secondary Medical:	Ramzi Dagher-John Johnson 1-9-06
Statistical:	
Pharmacology:	Haleh Mahloogi
Statistical Pharmacology:	
Chemistry:	Xiao Chen
Environmental Assessment (if needed):	
Biopharmaceutical:	Angela Men
Microbiology, sterility:	John Metcalfe
Microbiology, clinical (for antimicrobial products only):	
DSI:	
Regulatory Project Management:	Paul Zimmerman
Other Consults:	

Per reviewers, are all parts in English or English translation? YES NO
If no, explain:

CLINICAL FILE REFUSE TO FILE

- Clinical site inspection needed? YES NO
- Advisory Committee Meeting needed? YES, date if known _____ NO
- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? N/A YES NO

CLINICAL MICROBIOLOGY N/A FILE REFUSE TO FILE
STATISTICS N/A FILE REFUSE TO FILE

BIOPHARMACEUTICS	FILE <input checked="" type="checkbox"/>	REFUSE TO FILE <input type="checkbox"/>
• Biopharm. inspection needed?		YES <input type="checkbox"/> NO <input type="checkbox"/>
PHARMACOLOGY	N/A <input type="checkbox"/> FILE <input checked="" type="checkbox"/>	REFUSE TO FILE <input type="checkbox"/>
• GLP inspection needed?		YES <input type="checkbox"/> NO <input checked="" type="checkbox"/>
CHEMISTRY	FILE <input checked="" type="checkbox"/>	REFUSE TO FILE <input type="checkbox"/>
• Establishment(s) ready for inspection?		YES <input checked="" type="checkbox"/> NO <input type="checkbox"/>
• Microbiology		YES <input checked="" type="checkbox"/> NO <input type="checkbox"/>

ELECTRONIC SUBMISSION:
Any comments:

REGULATORY CONCLUSIONS/DEFICIENCIES:
(Refer to 21 CFR 314.101(d) for filing requirements.)

- The application is unsuitable for filing. Explain why:
- The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.
- No filing issues have been identified.
- Filing issues to be communicated by Day 74. List (optional):

ACTION ITEMS:

- If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.
- If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
- Convey document filing issues/no filing issues to applicant by Day 74.

PM will schedule monthly team meetings and begin weekly labeling meetings in April 2006

Paul Zimmerman
Regulatory Project Manager, HFD-

Appendix A to NDA Regulatory Filing Review

An application is likely to be a 505(b)(2) application if:

- (3) it relies on literature to meet any of the approval requirements (unless the applicant has a written right of reference to the underlying data)
- (4) it relies on the Agency's previous approval of another sponsor's drug product (which may be evidenced by reference to publicly available FDA reviews, or labeling of another drug sponsor's drug product) to meet any of the approval requirements (unless the application includes a written right of reference to data in the other sponsor's NDA)
- (5) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)
- (6) it seeks approval for a change from a product described in an OTC monograph and relies on the monograph to establish the safety or effectiveness of one or more aspects of the drug product for which approval is sought (see 21 CFR 330.11).

Products that may be likely to be described in a 505(b)(2) application include combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations), OTC monograph deviations, new dosage forms, new indications, and new salts.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, please consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

**Appendix B to NDA Regulatory Filing Review
Questions for 505(b)(2) Applications**

1. Does the application reference a listed drug (approved drug)? YES NO

If "No," skip to question 3.

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #(s): NDA 50-778 for Ellence (epirubicin hydrochloride injection) for non-clinical and clinical studies for safety and effectiveness

3. The purpose of this and the questions below (questions 3 to 5) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval and that should be referenced as a listed drug in the pending application.

- (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved?

YES NO

(Pharmaceutical equivalents are drug products in identical dosage forms that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; and (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))

If "No," skip to question 4. Otherwise, answer part (b).

- (b) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)? YES NO
(The approved pharmaceutical equivalent(s) should be cited as the listed drug(s).)

If "Yes," skip to question 6. Otherwise, answer part (c).

- (c) Have you conferred with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007)? YES NO

If "No," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.

4. (a) Is there a pharmaceutical alternative(s) already approved? YES NO

(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

If "No," skip to question 5. Otherwise, answer part (b).

- (b) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? YES NO
(The approved pharmaceutical alternative(s) should be cited as the listed drug(s).)

NOTE: If there is more than one pharmaceutical alternative approved, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007) to determine if the appropriate pharmaceutical alternatives are referenced.

If "Yes," skip to question 6. Otherwise, answer part (c).

- (c) Have you conferred with the Director, Division of Regulatory Policy II, ORP? YES NO

If "No," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.

5. (a) Is there an approved drug product that does not meet the definition of "pharmaceutical equivalent" or "pharmaceutical alternative," as provided in questions 3(a) and 4(a), above, but that is otherwise very similar to the proposed product?

YES NO

If "No," skip to question 6.

If "Yes," please describe how the approved drug product is similar to the proposed one and answer part (b) of this question. Please also contact the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007), to further discuss.

- (b) Is the approved drug product cited as the listed drug? YES NO

6. Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution"). This application is for a lyophilized formulation requiring reconstitution prior to administration, whereas the listed drug, Ellence, is a ready to use solution. This application's proposed lyophilized product differs in inactive ingredients from the listed drug. Lactose monohydrate is not present in the listed drug. The listed drug's inactives, water for injection, sodium chloride and hydrochloric acid are not contained this application's proposed lyophilized product.

7. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA will refuse-to-file such NDAs (see 21 CFR 314.101(d)(9)).) YES NO

8. Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application should be refused for filing under 21 CFR 314.101(d)(9)). YES NO

9. Is the rate at which the product's active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))? If yes, the application should be refused for filing under 21 CFR 314.101(d)(9). YES NO

10. Are there certifications for each of the patents listed for the listed drug(s)? YES NO

11. Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

- 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

Patent number(s):

- 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)
Patent number(s):
- 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)
Patent number(s):
- 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)
Patent number(s):

NOTE: IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must **subsequently** submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]. The applicant must also submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)].

- 21 CFR 314.50(i)(1)(ii): No relevant patents.
- 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)
Patent number(s):
- 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).
Patent number(s):
- Written statement from patent owner that it consents to an immediate effective date upon approval of the application.
Patent number(s):

12. Did the applicant:

- Identify which parts of the application rely on information (e.g. literature, prior approval of another sponsor's application) that the applicant does not own or to which the applicant does not have a right of reference?
YES NO
- Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity?
YES NO
- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug?
N/A YES NO

- Certify that it is seeking approval only for a new indication and not for the indications approved for the listed drug if the listed drug has patent protection for the approved indications and the applicant is requesting only the new indication (21 CFR 314.54(a)(1)(iv)).?
N/A YES NO

13. If the (b)(2) applicant is requesting 3-year exclusivity, did the applicant submit the following information required by 21 CFR 314.50(j)(4):

- Certification that at least one of the investigations included meets the definition of "new clinical investigation" as set forth at 314.108(a).
YES NO
- A list of all published studies or publicly available reports that are relevant to the conditions for which the applicant is seeking approval.
YES NO
- EITHER
The number of the applicant's IND under which the studies essential to approval were conducted.

IND# _____ NO

OR

A certification that the NDA sponsor provided substantial support for the clinical investigation(s) essential to approval if it was not the sponsor of the IND under which those clinical studies were conducted?

YES NO

3. Has the Associate Director for Regulatory Affairs, OND, been notified of the existence of the (b)(2) application?

YES NO

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

/s/

Paul Zimmerman
5/19/2006 11:02:01 AM
CSO

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information		
NDA 50-870	Efficacy Supplement Type SE-	Supplement Number
Drug: epirubicin hydrochloride for injection		Applicant: Mayne Pharma (USA) Inc.
RPM: Paul Zimmerman		HFD-150 DDOP Phone # 3017861489
<p>Application Type: () 505(b)(1) (<input checked="" type="checkbox"/>) 505(b)(2) (This can be determined by consulting page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)</p> <p>If this is a 505(b)(2) application, please review and confirm the information previously provided in Appendix B to the NDA Regulatory Filing Review. Please update any information (including patent certification information) that is no longer correct.</p> <p>() Confirmed and/or corrected</p>	<p>Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)):</p> <p>NDA 50-778 for Ellence (epirubicin hydrochloride injection)</p>	
❖ Application Classifications:		
<ul style="list-style-type: none"> • Review priority 		(<input checked="" type="checkbox"/>) Standard () Priority
<ul style="list-style-type: none"> • Chem class (NDAs only) 		5
<ul style="list-style-type: none"> • Other (e.g., orphan, OTC) 		NA
❖ User Fee Goal Dates		
		8-19-06
❖ Special programs (indicate all that apply)		
		() None Subpart H () 21 CFR 314.510 (accelerated approval) () 21 CFR 314.520 (restricted distribution) () Fast Track () Rolling Review () CMA Pilot 1 () CMA Pilot 2
❖ User Fee Information		
<ul style="list-style-type: none"> • User Fee 		() Paid UF ID number
<ul style="list-style-type: none"> • User Fee waiver 		() Small business () Public health () Barrier-to-Innovation () Other (specify)
<ul style="list-style-type: none"> • User Fee exception 		() Orphan designation (<input checked="" type="checkbox"/>) No-fee 505(b)(2) (see NDA Regulatory Filing Review for instructions) () Other (specify)
Application Integrity Policy (AIP)		
<ul style="list-style-type: none"> • Applicant is on the AIP 		() Yes (<input checked="" type="checkbox"/>) No

(Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).

If "No," continue with question (5).

- (5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?

Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).

If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).

If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.

❖ Exclusivity (approvals only)	
<ul style="list-style-type: none"> • Exclusivity summary • Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.) 	
<ul style="list-style-type: none"> • Is there existing orphan drug exclusivity protection for the "same drug" for the proposed indication(s)? Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification. 	<p><input checked="" type="checkbox"/> Yes, Application # 50-778 _____</p> <p><input type="checkbox"/> No</p>
❖ Administrative Reviews (Project Manager, ADRA) (indicate date of each review)	

General Information

General Information	
<ul style="list-style-type: none"> Proposed action 	() AP (X) TA () AE () NA
<ul style="list-style-type: none"> Previous actions (specify type and date for each action taken) 	none
<ul style="list-style-type: none"> Status of advertising (approvals only) 	() Materials requested in AP letter () Reviewed for Subpart H
❖ Public communications	
<ul style="list-style-type: none"> Press Office notified of action (approval only) 	() Yes (X) Not applicable
<ul style="list-style-type: none"> Indicate what types (if any) of information dissemination are anticipated 	() None () Press Release () Talk Paper () Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
<ul style="list-style-type: none"> Division's proposed labeling (only if generated after latest applicant submission of labeling) 	
<ul style="list-style-type: none"> Most recent applicant-proposed labeling 	
<ul style="list-style-type: none"> Original applicant-proposed labeling 	
<ul style="list-style-type: none"> Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings (indicate dates of reviews and meetings) 	
<ul style="list-style-type: none"> Other relevant labeling (e.g., most recent 3 in class, class labeling) 	
❖ Labels (immediate container & carton labels)	
<ul style="list-style-type: none"> Division proposed (only if generated after latest applicant submission) 	
<ul style="list-style-type: none"> Applicant proposed 	
<ul style="list-style-type: none"> Reviews 	
❖ Post-marketing commitments	
<ul style="list-style-type: none"> Agency request for post-marketing commitments 	N/A
<ul style="list-style-type: none"> Documentation of discussions and/or agreements relating to post-marketing commitments 	
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	
❖ Memoranda and Telecons	
❖ Minutes of Meetings	
<ul style="list-style-type: none"> EOP2 meeting (indicate date) 	no
<ul style="list-style-type: none"> Pre-NDA meeting (indicate date) 	5-19-04
<ul style="list-style-type: none"> Pre-Approval Safety Conference (indicate date; approvals only) 	no
<ul style="list-style-type: none"> Other 	
❖ Advisory Committee Meeting	
<ul style="list-style-type: none"> Date of Meeting 	NA
<ul style="list-style-type: none"> 48-hour alert 	
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	

Summary Application Review	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) (indicate date for each review)	
Clinical Information	
❖ Clinical review(s) (indicate date for each review)	
❖ Microbiology (efficacy) review(s) (indicate date for each review)	
❖ Safety Update review(s) (indicate date or location if incorporated in another review)	
❖ Risk Management Plan review(s) (indicate date/location if incorporated in another rev)	
❖ Pediatric Page (separate page for each indication addressing status of all age groups)	
❖ Demographic Worksheet (NME approvals only)	
❖ Statistical review(s) (indicate date for each review)	NA
❖ Biopharmaceutical review(s) (indicate date for each review)	3-20-06
❖ Controlled Substance Staff review(s) and recommendation for scheduling (indicate date for each review)	
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	NA
• Bioequivalence studies	
CMC Information	
❖ CMC review(s) (indicate date for each review)	
❖ Environmental Assessment	
• Categorical Exclusion (indicate review date)	
• Review & FONSI (indicate date of review)	
• Review & Environmental Impact Statement (indicate date of each review)	
❖ Microbiology (validation of sterilization & product sterility) review(s) (indicate date for each review)	
❖ Facilities inspection (provide EER report)	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ Methods validation	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested
Nonclinical/Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	4-19-06
❖ Nonclinical inspection review summary	
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	
❖ CAC/ECAC report	

Appendix A to NDA/Efficacy Supplement Action Package Checklist

An application is likely to be a 505(b)(2) application if:

- (1) it relies on literature to meet any of the approval requirements (unless the applicant has a written right of reference to the underlying data)
- (2) it relies on the Agency's previous approval of another sponsor's drug product (which may be evidenced by reference to publicly available FDA reviews, or labeling of another drug sponsor's drug product) to meet any of the approval requirements (unless the application includes a written right of reference to data in the other sponsor's NDA)
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)
- (4) it seeks approval for a change from a product described in an OTC monograph and relies on the monograph to establish the safety or effectiveness of one or more aspects of the drug product for which approval is sought (see 21 CFR 330.11).

Products that may be likely to be described in a 505(b)(2) application include combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations), OTC monograph deviations, new dosage forms, new indications, and new salts.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, please consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 50-807

Mayne Pharma (USA) Inc.
Attention: Steve Richardson
Director, Regulatory and Medical Affairs
Mack-Cali Centre II, Second Floor
650 From Road
Paramus, NJ 07652

Dear Mr. Richardson:

Please refer to your July 15, 2005 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Epirubicin Hydrochloride for Injection 50 mg, 200mg.

On May 1, 2006, we received your April 28, 2006 major amendment to this application. The receipt date is within 3 months of the user fee goal date. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is August 19, 2006.

If you have any questions, call me at 301-796-1489.

Sincerely,

{See appended electronic signature page}

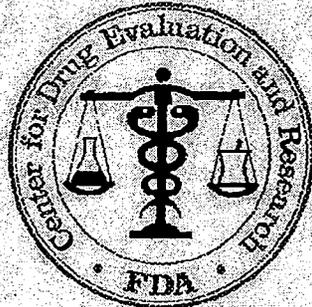
Paul Zimmerman
Project Manager
Division of Drug Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

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

/s/

Paul Zimmerman
5/9/2006 09:19:49 AM

FOOD AND DRUG ADMINISTRATION OFFICE OF ONCOLOGY DRUG PRODUCTS



DIVISION OF DRUG ONCOLOGY PRODUCTS

10903 New Hampshire Avenue
Silver Spring, Maryland 20993

The address for regulatory submissions is FDA/CDER/Division of Drug Oncology Products
5901-B Ammendale Road, Beltsville, MD 20705-1266

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PHONE: 301-796-1489 FAX: 301-796-9845

TO: Steve Richardson/Mayne Pharma
201-225-5530

FROM: Paul F. Zimmerman, Project Manager

Total number of pages, including cover sheet: 2

Date: April 25, 2006

COMMENTS: NDA 50-807 for Epirubicin Hydrochloride for Injection

As discussed by telephone today, the FDA review team notes, given the due date for this application, that complete and adequate responses to our requests concerning this application are needed by April 28, 2006. The application may likely be otherwise approvable.

In addition please address the following.

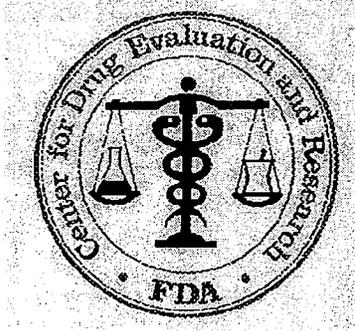
We note in your 3-23-06 submission that you agreed to the correction of the typographical errors,



In HOW SUPPLIED, make the following deletion.



FOOD AND DRUG ADMINISTRATION OFFICE OF ONCOLOGY DRUG PRODUCTS



DIVISION OF DRUG ONCOLOGY PRODUCTS

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PHONE: 301-796-1489 FAX: 301-796-9845

TO: Steve Richardson/Mayne Pharma
201-225-5530

FROM: Paul F. Zimmerman, Project Manager

Total number of pages, including cover sheet: 3

Date: April 18, 2006

COMMENTS: NDA 50-807 for Epirubicin Hydrochloride for Injection

Please address the following. Additional comments may be provided as our review continues.

Drug Substance:

1. DMF — is currently inadequate to support NDA 50-807. A letter containing deficiencies and comments has been conveyed to the DMF holder.

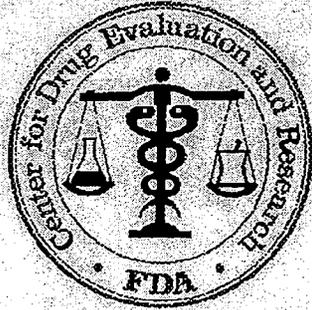
2 Page(s) Withheld

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

 § 552(b)(4) Draft Labeling

 § 552(b)(5) Deliberative Process

FOOD AND DRUG ADMINISTRATION OFFICE OF ONCOLOGY DRUG PRODUCTS



DIVISION OF DRUG ONCOLOGY PRODUCTS

10903 New Hampshire Avenue
Silver Spring, Maryland 20993

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PHONE: 301-796-1489 FAX: 301-796-9845

TO: Steve Richardson/Mayne Pharma
201-225-5530

FROM: Paul F. Zimmerman, Project Manager

Total number of pages, including cover sheet: 2

Date: April 13, 2006

COMMENTS: NDA 50-807 for Epirubicin Hydrochloride for Injection

Please address the following. Additional comments may be provided as our review continues.

Regarding our communications concerning potential microbial growth, please do one of the following:

- remove the labeling information regarding a hold period of 24 hours at 25 degrees C following reconstitution.
- provide data from studies that demonstrates that the drug product will not support growth of microorganisms over the stated hold period. (We can speak with you about study design, if needed.)

1 Page(s) Withheld

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

 § 552(b)(4) Draft Labeling

 § 552(b)(5) Deliberative Process

CONSULTATION RESPONSE

**DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(DMETS; HFD-420)**

DATE RECEIVED:

March 8, 2006

DATE OF DOCUMENT:

July 15, 2005

DESIRED COMPLETION DATE:

April 3, 2006

PDUFA DATE:

May 19, 2006

ODS CONSULT #: 06-0094

TO: Robert Justice, MD
Director, Division of Drug Oncology Products
HFD-150

THROUGH: Linda Kim-Jung, PharmD., Team Leader
Denise Toyer, PharmD, Deputy Director
Carol Holquist, RPh., Director
Division of Medication Errors and Technical Support, HFD-420

FROM: Linda M. Wisniewski, RN, Safety Evaluator
Division of Medication Errors and Technical Support, HFD-420

PRODUCT NAME:

Epirubicin Hydrochloride for Injection
50 mg and 200 mg

NDA# 50-807

NDA SPONSOR:

Mayne Pharma., Inc.

SAFETY EVALUATOR: Linda M. Wisniewski, RN

RECOMMENDATIONS:

DMETS recommends implementation of the label and labeling revisions outlined in section II of this review that might lead to safer use of the product. We would be willing to revisit these issues if the Division receives another draft of the labeling from the manufacturer.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Diane Smith, project manager, at 301-796-0538.

Division of Medication Errors and Technical Support (DMETS)
Office of Drug Safety
HFD-420; PKLN Rm. 6-34
Center for Drug Evaluation and Research

LABEL AND LABELING REVIEW

DATE OF REVIEW: March 15, 2006

NDA#: 50-807

NAME OF DRUG: Epirubicin Hydrochloride for Injection
50 mg and 200 mg

NDA HOLDER: Mayne Pharma, Inc.

I. INTRODUCTION:

This consult was written in response to a request from the Division of Drug Oncology Products for assessment of the labels and labeling for Epirubicin Hydrochloride for Injection. The sponsor provided draft container labels, carton and package insert labeling for review and comment. The reference listed drug for this 505b2 application is Ellence, NDA 50-778.

PRODUCT INFORMATION

Epirubicin Hydrochloride for Injection is an anthracycline cytotoxic agent, intended for intravenous administration. Epirubicin Hydrochloride for Injection is supplied as a sterile, orange-red, lyophilized powder in single-dose vials containing 50 mg or 200 mg of epirubicin. It is indicated as a component of adjuvant therapy in patients with evidence of axillary node tumor involvement following resection of primary breast cancer. Starting doses range from 100 mg/m² to 120 mg/m² and subsequent doses range from 60 mg/m² to 100 mg/m². Epirubicin HCl for Injection is given in repeated three to four week cycles.

II. LABELING, PACKAGING, AND SAFETY RELATED ISSUES:

In the review of the container labels, carton and insert labeling of Epirubicin Hydrochloride for Injection, DMETS has attempted to focus on safety issues relating to possible medication errors. DMETS has identified the following areas of possible improvement, which might minimize potential user error.

A. GENERAL COMMENT

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B. CONTAINER LABEL (50 mg and 200 mg)

└

┌

C. CARTON LABELING (50 mg and 200 mg)

└

D. INSERT LABELING

└

No comments.

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this page is the manifestation of the electronic signature.**

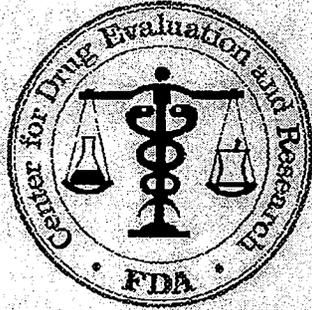
/s/

Linda Wisniewski
4/12/2006 12:58:21 PM
DRUG SAFETY OFFICE REVIEWER

Linda Kim-Jung
4/12/2006 01:12:19 PM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
4/12/2006 01:49:35 PM
DRUG SAFETY OFFICE REVIEWER
Also signing for Carol Holquist, Director DMETS, in her
absence

FOOD AND DRUG ADMINISTRATION OFFICE OF ONCOLOGY DRUG PRODUCTS



DIVISION OF DRUG ONCOLOGY PRODUCTS

10903 New Hampshire Avenue
Silver Spring, Maryland 20993

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PHONE: 301-796-1489 FAX: 301-796-9845

TO: Steve Richardson/Mayne Pharma
201-225-5530

FROM: Paul F. Zimmerman, Project Manager

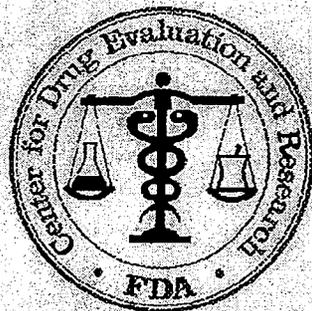
Total number of pages, including cover sheet: 1

Date: March 21, 2006

COMMENTS: NDA 50-807 for Epirubicin Hydrochloride for Injection

We note your previous agreement to submit stability update with 12 months data at 8 months of the NDA submission. Have you submitted this or are you planning to do so soon?

FOOD AND DRUG ADMINISTRATION OFFICE OF ONCOLOGY DRUG PRODUCTS



DIVISION OF DRUG ONCOLOGY PRODUCTS

10903 New Hampshire Avenue
Silver Spring, Maryland 20993

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5901-B Ammendale Road, Beltsville, MD 20705-1266

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PHONE: 301-796-1489 FAX: 301-796-9845

TO: Steve Richardson/Mayne Pharma
201-225-5530

FROM: Paul F. Zimmerman, Project Manager

Total number of pages, including cover sheet: 2

Date: March 13, 2006

COMMENTS: NDA 50-807 for Epirubicin Hydrochloride for Injection

Regarding NDA 50-807, the following is taken from page 23 of 24 of the proposed package insert:

✓

✓

It is noted that the proposed labeling states that the reconstituted solution is stable for 24 hours at 25°C. Have studies been performed to determine whether the reconstituted drug product is capable of supporting microbial growth over the 24 hour storage period at 25°C? If so, where is the location of these data in the subject submission? If such studies have not been performed, please provide a rationale.

In addition, it is noted that the stated diluent volume (—mL) for reconstitution of the 50 mg vial is incorrect. Please comment.

**APPEARS THIS WAY
ON ORIGINAL**



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 50-807

Mayne Pharma (USA) Inc.
Attention: Steve Richardson
Director, Regulatory and Medical Affairs
Mack-Cali Centre II, Second Floor
650 From Road
Paramus, NJ 07652

Dear Mr. Richardson:

Please refer to your July 15, 2005 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Epirubicin Hydrochloride for Injection lyophilized, 50mg/vial, 200 mg/vial.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on September 17, 2005 in accordance with 21 CFR 314.101(a).

At this time, we have not identified any potential filing review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

If you have any questions, call Paul Zimmerman, Regulatory Project Manager, at 301-594-5775.

Sincerely,

{See appended electronic signature page}

Paul Zimmerman, R.Ph.
Regulatory Project Manager
Division of Drug Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

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this page is the manifestation of the electronic signature.**

/s/

Paul Zimmerman
9/22/2005 11:33:58 AM

PRESCRIPTION DRUG USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: <http://www.fda.gov/cder/pdufa/default.htm>

1. APPLICANT'S NAME AND ADDRESS Mayne Pharma (USA) Inc. Mack Cali Centre II, 2nd Floor 650 From Road Paramus, NJ 07652	4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER
2. TELEPHONE NUMBER (Include Area Code) (201) 225-5514	5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM. IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW: <input type="checkbox"/> THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION. <input checked="" type="checkbox"/> THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO: NDA 50-778 (APPLICATION NO. CONTAINING THE DATA).
3. PRODUCT NAME Epirubicin Hydrochloride for Injection	6. USER FEE I.D. NUMBER 57575

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

<input type="checkbox"/> A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory)	<input checked="" type="checkbox"/> A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE (See item 7, reverse side before checking box.)
<input type="checkbox"/> THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act (See item 7, reverse side before checking box.)	<input type="checkbox"/> THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY (Self Explanatory)

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? YES NO
(See Item 8, reverse side if answered YES)

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services Food and Drug Administration CBER, HFM-99 1401 Rockville Pike Rockville, MD 20852-1448	Food and Drug Administration CDER, HFD-94 and 12420 Parklawn Drive, Room 3046 Rockville, MD 20852	An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.
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SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE 	TITLE Director, Regulatory and Medical Affairs	DATE 06/21/2005
---	---	--------------------

TELECON MINUTES

TELECON DATE: May 19, 2004 **TIME:** 11:00 **LOCATION:** B

IND: 69,448 **Meeting Request Submission Date:** 4-6-04
FDA Response Date: 4-16-04
Briefing Document Submission Date: 4-6-04

DRUG: epirubicin freeze-dried **INDICATION:** adjuvant breast cancer

SPONSOR: Mayne Pharmaceuticals **TYPE of TELECON:** pre-IND/NDA

FDA PARTICIPANTS: Grant Williams, M.D., Dep. Dir., DODP
Ramzi Dagher, M.D., Medical Team Leader, DODP
Patricia Cortazar, M.D., Medical Officer, DODP
Nallaperumal Chidambaram, Ph.D., Dep. Dir., DNDCI
Xiao Chen, Ph.D., Chemistry Reviewer, DODP
David Morse, Ph.D., Pharm. Supervisor, DODP
Haleh Saber-Mahloogi, Ph.D., Pharmacologist, DODP
Brian Booth, Ph.D., Acting Clin. Phar./Biopharm. TL, DODP
Sophia Abraham, Ph.D., Clin. Pharm. Reviewer, DODP
Dotti Pease, Project Manager, DODP

SPONSOR: Mr. Steve Richardson, Director, Regulatory Affairs, Paramus, NJ
Mr. Aroon D. Mankad, Asst. Manager, Reg. Affairs, Paramus, NJ
Dr. Fiona Bennett, Manager, Regulatory Affairs, Mulgrave, Australia
Ms. Rachel Milburn, Sr. Regulatory Affairs Assoc, Mulgrave, Australia
Mr. Michael Robertson, Section Leader, Prod. Dev., Mulgrave, Australia
Dr. Clive Blower, Manager, Product Dev. Group, Mulgrave, Australia

MEETING OBJECTIVES: Discuss proposed 505(b)(2) NDA and sponsor's questions

BACKGROUND: The proposed freeze-dried formulation of epirubicin will have different inactive ingredients that make the product ineligible for an ANDA; therefore, sponsor proposes a 505(b)(2) application with reliance on the Ellence (P&U) clinical and preclinical data. Ellence is protected under Orphan Exclusivity until 9-15-06; however, other epirubicin applications may be accepted and approved at any time prior to then with a tentative approval, i.e., delayed effective date. This telecon was scheduled mainly to discuss whether the product qualified for 505(b)(2) and the proposed stability program.

The FDA draft responses were e-mailed to the sponsor on May 14, and Mayne elected to have the telecon for clarification. Mayne also submitted additional material on May 18 which was not completely reviewed prior to the telecon. Discussion is indicated in italics.

QUESTIONS for DISCUSSION with FDA RESPONSE and DECISIONS REACHED:

1. Can Mayne reference the FDA's finding of safety and effectiveness for NDA 50-778 in its 505(b)(2) application?

FDA - Yes, assuming that this application is not affected by the pending litigation re: 505(b)(2)s. The Ellence application is protected by Orphan Exclusivity until September 15, 2006, as noted in your meeting package; therefore, your application could not be approved until Ellence exclusivity expires.

DISCUSSION: The additional submission of May 18, 2004 will be reviewed and FDA will convey any comments.

2. As discussed in the Attachment 3, would the Agency allow Mayne to submit a 505(b)(2) application with stability data on one representative batch for each presentation? Mayne will commit to monitor stability of three commercial batches of each presentation.

FDA - No. You should provide stability data for three batches of the drug product, preferably containing 12 months long term and 6 months accelerated data in the NDA. In addition, you should also provide complete Chemistry, Manufacturing, and Control information for both drug substance and drug product. The CMC information for drug substance can either be provided in the NDA or by cross referencing an NDA and/or DMF.

Please note that any new impurities may need to be qualified for safety.

DISCUSSION: Two dosage strengths are proposed - 50 mg and 200 mg, packaged in a slightly different container/closure. A bracketing proposal for stability should include a minimum of two batches for each strength. Laboratory batches are not acceptable; however, we could accept pilot scale batches or full scale batches. A 505(b)(2) is considered an NDA, not an ANDA; therefore, stability requirements are for NDAs, not ANDAs.

3. Does the Agency agree with Mayne's proposed content of the 505(b)(2) application?

FDA - Yes. We note that the active ingredient is the same and will be administered at the same dose level as that for Ellence. Moreover, the dose, schedule, and route of administration of the freeze-dried formulation seems to be the same as those described in the labeling for Ellence. Changes in the inactive ingredients as described in the package do not appear to require additional animal toxicity studies. You may reference the nonclinical and clinical data generated with Pharmacia's formulations. See #1.

DISCUSSION: Sponsor inquired about how to submit the clinical and preclinical sections of the NDA. FDA will forward any available guidance in this regard.

ADDITIONAL FDA COMMENTS:

Regarding your comment on User Fee waiver, it is our understanding that a one half User Fee is charged for NDAs without clinical data. You should check with our User Fee staff at 301 443-5532.

ACTION ITEMS:

1. Sponsor to submit a bracketing proposal for the stability program, which FDA will review in two weeks.
2. FDA will review the May 18, 2004 submission and convey any additional comments we may have.
3. FDA will send Mayne the guidance on 505(b)(2) submissions. Website is <http://www.fda.gov/cder/guidance/2853dft.htm>
4. The NDA submission is planned for 1st quarter of 2005.

Dotti Pease
Chief, Project Management Staff

Concurrence Chair: _____
Grant Williams, M.D.
Deputy Director

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

/s/

Grant Williams
6/2/04 05:31:25 PM

1. Can Mayne reference the FDA's finding of safety and effectiveness for NDA 50-778 in its 505(b)(2) application?

FDA - Yes, assuming that this application is not affected by the pending litigation re: 505(b)(2)s. The Ellence application is protected by Orphan Exclusivity until September 15, 2006, as noted in your meeting package; therefore, your application could not be approved until Ellence exclusivity expires.

2. As discussed in the Attachment 3, would the Agency allow Mayne to submit a 505(b)(2) application with stability data on one representative batch for each presentation? Mayne will commit to monitor stability of three commercial batches of each presentation.

FDA - No. You should provide stability data for three batches of the drug product, preferably containing 12 months long term and 6 months accelerated data in the NDA. In addition, you should also provide complete Chemistry, Manufacturing, and Control information for both drug substance and drug product. The CMC information for drug substance can either be provided in the NDA or by cross referencing an NDA and/or DMF.

Please note that any new impurities may need to be qualified for safety.

3. Does the Agency agree with Mayne's proposed content of the 505(b)(2) application?

FDA - Yes. We note that the active ingredient is the same and will be administered at the same dose level as that for Ellence. Moreover, the dose, schedule, and route of administration of the freeze-dried formulation seems to be the same as those described in the labeling for Ellence. Changes in the inactive ingredients as described in the package do not appear to require additional animal toxicity studies. You may reference the nonclinical and clinical data generated with Pharmacia's formulations. See #1.

ADDITIONAL FDA COMMENTS:

Regarding your comment on User Fee waiver, it is our understanding that a one half User Fee is charged for NDAs without clinical data. You should check with our User Fee staff at 301 443-5532.



Date: May 18, 2004

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**RE: Type C Meeting Request - Epirubicin Hydrochloride for Injection
(Freeze-Dried Formulation)**

Dear Ms. Pease:

Thank you for your responses to our questions regarding registration of Epirubicin Hydrochloride for Injection, as received May 14th, 2004. Based on these responses, we wish to proceed with the scheduled teleconference on May 19th, specifically to discuss the response to Question 2. This question relates to the stability data requirements for the submission. Mayne still maintains that it should be acceptable to provide a reduced stability data at the time of submission, and it is the intent of this letter to reiterate the company's rationale, and provide a basis for discussions during our teleconference.

Background:

As discussed in our initial meeting request, it is the company's intent to register and launch a generic version of the reference-listed drug (RLD) Ellence[®] by the expiration of orphan drug exclusivity in September 2006. The company plans to develop a lyophilized version of the RLD to allow for the entry of generic competition at the expiration of exclusivity, given that there are various non-Orange Book listed patents preventing solution versions of the generic product from being marketed until August 2007.

Mayne's product differs to the RLD in terms of dosage form (lyophilized versus ready-to-use solution) and formulation (changes to inactive ingredients). The change in dosage form, *per se*, would allow for filing of the application via Section 505(j) of the Food, Drug and Cosmetic Act (FDCA)¹. It is the change of inactive ingredients, as restricted under 21 CFR 314.94(a)(9), which requires the application to be filed pursuant to section 505(b)(2) of the FDCA.

Mayne consider that the changes to formulation are minor, and in fact impart an improved stability profile compared to the RLD, and further support that stability data requirements for submission should be considered in light of the requirements for an

¹ Based on suitability petition.

**Attachment 1: Comparative Data between Epirubicin HCl for Injection
(laboratory scale formulation) and RLD Ellence®.**

	Epirubicin HCl for Injection (50 mg / vial)		Ellence®¹ (50 mg / 25 mL)
	Initial	40°C/75% RH, 4 weeks	
Assay (%)			
Impurity			

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+

1.3

ADMINISTRATIVE DOCUMENTS

a. Administrative Documents

Environmental Assessment

CATEGORICAL EXCLUSION FROM THE REQUIREMENT OF AN ENVIRONMENTAL ASSESSMENT

The drug product covered by this application is identical, similar or related in chemical structure, known pharmaceutical properties, and indications for use to drugs which are already being marketed, and there is no reason to conclude that marketing of such additional drug products will change the overall use pattern of the active moiety.

Pursuant to 21 CFR 25.31(a), Mayne Pharma (USA) Inc. hereby claims a categorical exclusion from the requirement of an Environmental Assessment.