

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**22-474**

**ADMINISTRATIVE and CORRESPONDENCE**  
**DOCUMENTS**

## EXCLUSIVITY SUMMARY

NDA # 022474

SUPPL #

HFD # 580

Trade Name Ella

Generic Name ulipristal acetate

Applicant Name Laboratoire HRA Pharma

Approval Date, If Known August 13, 2010

### 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

505(b)(1)

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?

5

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#

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



Investigation #1  
!  
!  
YES  ! NO   
Explain: ! Explain:

Investigation #2  
!  
!  
YES  ! NO   
Explain: ! 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:

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Name of person completing form: Pamela Lucarelli  
Title: Regulatory Health Project Manager  
Date: July 29, 2010

Name of Office/Division Director signing form: Julie Beitz  
Title: Office Director

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

| Application<br>Type/Number | Submission<br>Type/Number | Submitter Name            | Product Name              |
|----------------------------|---------------------------|---------------------------|---------------------------|
| NDA-22474                  | ORIG-1                    | LABORATOIRE<br>HRA PHARMA | Ella , Ulipristal Acetate |

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/s/  
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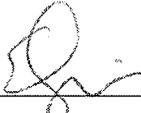
PAMELA LUCARELLI  
08/13/2010

JULIE G BEITZ  
08/13/2010

1.3.3            **DEBARMENT CERTIFICATION**

Debarment Certification

HRA Pharma 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.



\_\_\_\_\_  
Erin Gainer  
Chief Executive Officer

Sept 7, 2009

Date



17, rue de Pontoise  
95520 Osny – France  
T + 33 1 34 20 44 20  
F + 33 1 34 20 44 75

## **GMP Compliance and Debarment Certifications**

### **GMP Compliance Certification**

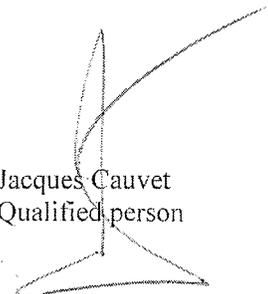
Osny Pharma SAS certifies that ULIPRISTAL ACETATE 30 mg TABLETS as described in this NDA are produced within GMP compliant facilities and specifically that the production, processing, labeling, control operations and warehouse operations of ULIPRISTAL ACETATE 30 mg TABLETS are in compliance with current good manufacturing practices (cGMP) as described in 21 CFR Parts 210 and 211.

Osny Pharma SAS declares that ULIPRISTAL ACETATE 30 mg TABLETS will be manufactured, tested and packaged as described in this NDA and that the material released to the US market will meet the requirements of this NDA.

### **Debarment Certification**

Osny Pharma SAS as the manufacturer of the ULIPRISTAL ACETATE 30 mg TABLETS certifies that it has not used and will not use, in any capacity, the services of any person debarred under the Generic Drug Enforcement Act of 1992 subsections (a) or (b) [section 306 (a) or (b)], in connection with this submission.

We also certify that within the past five years there have been no relevant convictions of the applicant and affiliated persons responsible for the development of this NDA, as described in Section 306 (a) and (b) of the 1992 Generic Drug Enforcement Act.



Jacques Cauvet  
Qualified person

## GMP Compliance and Debarment Certifications

### GMP Compliance Certification

Laboratorios LEÓN FARMA S.A. certifies that ULIPRISTAL ACETATE 30 mg TABLETS as described in this NDA are produced within GMP compliant facilities and specifically that the production, processing, labeling, control operations and warehouse operations of ULIPRISTAL ACETATE 30 mg TABLETS are in compliance with current good manufacturing practices (cGMP) as described in 21 CFR Parts 210 and 211.

Laboratorios LEÓN FARMA S.A declares that ULIPRISTAL ACETATE 30 mg TABLETS will be manufactured, tested and packaged as described in this NDA and that the material released to the US market will meet the requirements of this NDA.

Annual updates to this NDA will be submitted to FDA and changes to the manufacturing process, specifications or testing that require prior approval will not be instituted until approved by FDA.

### Debarment Certification

Laboratorios LEÓN FARMA S.A as the manufacturer of the ULIPRISTAL ACETATE 30 mg TABLETS certifies that it has not used and will not use, in any capacity, the services of any person debarred under the Generic Drug Enforcement Act of 1992 subsections (a) or (b) [section 306 (a) or (b)], in connection with this submission.

We also certify that within the past five years there have been no relevant convictions of the applicant and affiliated persons responsible for the development of this NDA, as described in Section 306 (a) and (b) of the 1992 Generic Drug Enforcement Act.

León, August 07, 2009



ALBERTO CARAZO FORNIELES  
QUALIFIED PERSON

### CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

- (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

|                        |  |  |
|------------------------|--|--|
| Clinical Investigators | Please see attached list of clinical investigators |  |
|                        |  |  |
|                        |  |  |

- (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

- (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

|  |                                  |
|--|----------------------------------|
| NAME<br>Erin Gainer  | TITLE<br>Chief Executive Officer |
| FIRM/ORGANIZATION<br>HRA Pharma  |                                  |
| SIGNATURE<br> | DATE<br>July 9 2009              |

#### Paperwork Reduction Act Statement

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. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right.

Department of Health and Human Services  
Food and Drug Administration  
5600 Fishers Lane, Room 14C-03  
Rockville, MD 20857

## Lucarelli, Pamela K

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**From:** Greeley, George  
**Sent:** Wednesday, July 21, 2010 3:17 PM  
**To:** Lucarelli, Pamela K  
**Cc:** Addy, Rosemary; Mathis, Lisa  
**Subject:** NDA 22-474 Ella

**Importance:** High

**Attachments:** 1\_Pediatric\_Record.pdf

Hi Pam,

The Ella (ulipristal acetate) partial waiver and extrapolation was reviewed by the PeRC PREA Subcommittee on June 30, 2010.

The Division presented a partial waiver because the disease/condition does not exist in children 0 to 11 years and the extrapolation of efficacy in patients 12 to 16 years of age.

The PeRC agreed with the Division to grant a partial waiver and the extrapolation of efficacy product. The pediatric record is attached reflecting the PeRC review for Ella.



1\_Pediatric\_Record  
.pdf (62 KB)...

Thank you.

George Greeley  
Regulatory Health Project Manager  
Pediatric and Maternal Health Staff  
FDA/CDER/OND  
10903 New Hampshire Avenue  
Bldg. 22, Room 6467  
Silver Spring, MD 20993-0002  
Phone: 301.796.4025  
Email: [george.greeley@fda.hhs.gov](mailto:george.greeley@fda.hhs.gov)

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Silver Spring, MD 20993

NDA 022474

**PROPRIETARY NAME REQUEST  
CONDITIONALLY ACCEPTABLE**

Laboratoire HRA Pharma  
c/o Target Health  
261 Madison Avenue  
New York, New York 10021

ATTENTION: Glen D. Park, Pharm.D.  
Sr. Director Clinical and Regulatory Affairs  
Target Health

Dear Dr. Park:

Please refer to your New Drug Application (NDA) dated October 14, 2009, received October 15, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ulipristal Acetate Tablets 30 mg.

We also refer to your November 4, 2009, correspondence, received November 6, 2009, requesting review of your proposed proprietary name, Ella. We have completed our review of the proposed proprietary name, Ella, and have concluded that it is acceptable.

The proposed proprietary name, Ella, will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you.

If **any** of the proposed product characteristics as stated in your November 4, 2009 submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Maria Wasilik, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-0567. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Pamela Lucarelli at (301) 796-3961.

Sincerely,

*Carol Holquist*  
Carol Holquist, RPh  
Director  
Division of Medication Error Prevention and Analysis  
Office of Surveillance and Epidemiology  
Center for Drug Evaluation and Research

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

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NDA-22474

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ORIG-1

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LABORATOIRE  
HRA PHARMA

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Ella , Ulipristal Acetate

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/s/  
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DENISE P TOYER on behalf of CAROL A HOLQUIST  
01/25/2010



NDA 22-474

**NDA ACKNOWLEDGMENT**

Laboratoire HRA Pharma  
C/o Target Health, Inc.  
Attention: Glen D. Park, Pharm.D.  
Senior Director, Clinical and Regulatory Affairs  
261 Madison Avenue, 24<sup>th</sup> Floor  
New York, NY 10016

Dear Mr. Park:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: ulipristal acetate 30 mg tablet

Date of Application: October 14, 2009

Date of Receipt: October 15, 2009

Our Reference Number: NDA 22-474

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on December 15, 2009 in accordance with 21 CFR 314.101(a).

Please note that you are responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) (42 USC §§ 282(i) and (j)), which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No. 110-85, 121 Stat. 904). Title VIII of FDAAA amended the PHS Act by adding new section 402(j) (42 USC § 282(j)), which expanded the current database known as ClinicalTrials.gov to include mandatory registration and reporting of results for applicable clinical trials of human drugs (including biological products) and devices. FDAAA requires that, at the time of submission of an application under section 505 of the FDCA, the application must be accompanied by a certification that all applicable requirements of 42 USC § 282(j) have been met. Where available, the certification must include the appropriate National Clinical Trial (NCT) control numbers. 42 USC 282(j)(5)(B). You did not include such certification when you submitted this application. You may use Form FDA 3674, *Certification of Compliance, under 42 U.S.C. § 282(j)(5)(B), with Requirements of ClinicalTrials.gov Data Bank*, to comply with the certification requirement. The form may be found at <http://www.fda.gov/opacom/morechoices/fdaforms/default.html>.

In completing Form FDA 3674, you should review 42 USC § 282(j) to determine whether the requirements of FDAAA apply to any clinical trials referenced in this application. Additional information regarding the certification form is available at:

[http://internet-dev.fda.gov/cder/regulatory/FDAAA\\_certification.htm](http://internet-dev.fda.gov/cder/regulatory/FDAAA_certification.htm). Additional information regarding Title VIII of FDAAA is available at:

<http://grants.nih.gov/grants/guide/notice-files/NOT-OD-08-014.html>. Additional information on registering your clinical trials is available at the Protocol Registration System website <http://prsinfo.clinicaltrials.gov/>.

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Reproductive and Urologic Products  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

If you have any questions, please call Pamela Lucarelli, Regulatory Health Project Manager at (301) 796-3961.

Sincerely,

Jennifer Mercier  
Chief, Project Management Staff  
Division of Reproductive and Urologic Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

| Application Type/Number | Submission Type/Number | Submitter Name | Product Name                             |
|-------------------------|------------------------|----------------|--|
| NDA-22474               | ORIG-1                 | HRA PHARMA LLC | ULIPRISTAL ACETATE (CDB-2914,BKB 101,VA2 |

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/s/

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JENNIFER L MERCIER  
10/22/2009



NDA 22-474

**INFORMATION REQUEST**

Laboratoire HRA Pharma  
c/o Target Health, Inc.  
Attention: Glen D. Park, Pharm.D.  
Senior Director, Clinical and Regulatory Affairs  
261 Madison Avenue, 24<sup>th</sup> Floor  
New York, NY 10016

Dear Mr. Park:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ulipristal acetate 30 mg tablet.

We are reviewing the Chemistry, Manufacturing and Controls sections 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.

1. Because your process involves a (b) (4), please include (b) (4) in the specification, unless justified.
2. Please define the "mean mass" in the stability specification with a test method and acceptance criterion. Clarify if the apparent increase of mean mass on stability is due to an (b) (4)
3. The proposed dissolution limit of  $Q = (b) (4)$  is not properly justified. Tighten the dissolution specification to  $Q = (b) (4)$  in 15 minutes.
4. Justify (b) (4) level described in the manufacturing process and proposed in the master batch record for Leon Farma.
5. In order to justify your plan to test for microbial limits at only the start and the end of stability and to ensure microbial purity before the end of the stability study, submit recent microbial limit testing results for long-term stability samples from both manufacturing sites. Alternatively, you may submit recent (b) (4) results for stability samples to justify microbial limits to date. Microbial testing should be conducted with the next stability samples pulled from those batches currently held in the stability program.
6. Please revise the proposed release testing of microbial contamination such that every 10th batch (after 10 consecutive batches are tested) will be tested, however, if the

number of production batches are less than 10 batches per year, at least 1 batch will be tested per year.

7. Provide information on the container/closure system for intended bulk storage of drug product and confirm that it the same as the container/closure used in the bulk storage studies. Otherwise provide a comparison table listing any differences including the storage conditions. Your application states that microbial contamination was one of the parameters investigated during the bulk storage studies. However, data from Leon Farma show only release results for microbial limit tests. Please submit the missing data.

To facilitate prompt review of your response, please also provide an electronic courtesy copy of your response to both Jeannie David, Regulatory Project Manager in the Office of New Drug Quality Assessment (Jeannie.David@fda.hhs.gov), and Pamela Lucarelli, Regulatory Project Manager the Office of New Drugs (Pamela.Lucarelli@fda.hhs.gov).

If you have any questions regarding this letter, contact Jeannie David, Regulatory Project Manager, at (301) 796-4247.

Sincerely,

*Moo-Jhong Rhee*

Moo-Jhong Rhee, Ph.D.  
Chief, Branch III  
Division of Pre-Marketing Assessment II  
Office New Drug Quality Assessment  
Center for Drug Evaluation and Research

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

NDA-22474

ORIG-1

LABORATOIRE  
HRA PHARMA

Ella , Ulipristal Acetate

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/s/  
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MOO JHONG RHEE

04/19/2010

Chief, Branch III



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service  
Food and Drug Administration  
Rockville, MD 20857

IND 49,381

Target Health, Inc.  
Attention: Glen D. Park, Pharm.D.  
Senior Director, Clinical and Regulatory Affairs  
261 Madison Avenue, 24<sup>th</sup> Floor  
New York, NY 10016

Dear Dr. Park:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for CDB-2914.

We also refer to the meeting between representatives of your firm and the FDA on December 12, 2008. The purpose of the meeting was to discuss the proposed new drug application (NDA) for CDB-2914 in emergency contraception.

We further refer to our previous communication of January 7, 2009, in which the Background section misstated that CDB-2914 should be taken within 72 hours of unprotected intercourse. CDB-2914 should be taken within 120 hours of unprotected intercourse.

A corrected copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, please call Pamela Lucarelli, Regulatory Health Project Manager at (301) 796-3961.

Sincerely,

Lisa Soule, M.D.  
Clinical Team Leader  
Division of Reproductive and Urologic Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

Enclosure - Meeting Minutes

**MEMORANDUM OF MEETING MINUTES**

**MEETING DATE:** December 12, 2008

**TIME:** 11:30 A.M. to 1:00 P.M.

**LOCATION:** Food and Drug Administration  
10903 New Hampshire Avenue, Conference Room 1315, Bldg 22  
Silver Spring, MD 20903

**APPLICATION:** IND 49,381

**DRUG NAME:** CDB-2914

**TYPE OF MEETING:** Type B, Pre-NDA

**MEETING CHAIR:** Lisa Soule, M.D.

**MEETING RECORDER:** Pamela Lucarelli

**FDA ATTENDEES:**

Scott Monroe, M.D. – Director, Division of Reproductive and Urologic Products (DRUP)  
Lisa Soule, M.D. – Clinical Team Leader, DRUP  
Ronald Orleans, M.D. – Medical Officer, DRUP  
Daniel Davis, M.D. – Medical Officer, DRUP  
Donna Christner, Ph.D. – Pharmaceutical Assessment Lead, Branch III, Division of Pre-Marketing Assessment II, Office of New Drug Quality Assessment  
Lynnda Reid, Ph.D. – Supervisor, Pharmacology/Toxicology, DRUP  
Jeffery Bray, Ph.D. – Pharmacologist/Toxicologist, DRUP  
Doanh Tran Ph.D. – Clinical Pharmacology Reviewer, Division of Clinical Pharmacology III (DCPIII) Office of Clinical Pharmacology (OCP)  
LaiMing Lee, Ph.D. – Clinical Pharmacology Reviewer, DCPIII, OCP  
Jennifer Mercier – Chief, Project Management Staff, DRUP  
Nenita Crisostomo, R.N. – Regulatory Health Project Manager, DRUP  
Pamela Lucarelli – Regulatory Health Project Manager, DRUP

**LABORATOIRE HRA PHARMA/TARGET HEALTH INC. ATTENDEES:**

Erin Gainer, Ph.D., MPH – Director, Research and Development, Laboratoire HRA Pharma  
André Ulmann, M.D., Ph.D. – CEO, Laboratoire HRA Pharma  
Anne-Laure Astecker, Pharm.D – Regulatory Affairs Officer, Laboratoire HRA Pharma  
Delphine Levy, M.D. – Clinical Research Medical Manager, Laboratoire HRA Pharma  
Henri Mathe – Clinical Operations Manager, Women's Health, Laboratoire HRA Pharma  
Helene Guillard, Pharm.D – Director, Quality and Pharmaceutical Affairs, Laboratoire HRA Pharma

Paul Fine, M.D. – Medical Director Phase 3 Principal Investigator, Planned Parenthood of Houston and Southeast Texas

(b) (4)

Glen Park, Pharm.D – Regulatory Affairs Consultant, Target Health Inc.

Diana Blithe, Ph.D. – Program Director Contraceptive Development, NICHD, NIH

(b) (4)

#### **BACKGROUND:**

CDB-2914 (ulipristal acetate) is being developed as an emergency contraceptive to be taken within 120 hours of unprotected intercourse. CDB-2914 is a progesterone receptor modulator that reversibly blocks the progesterone receptors in target tissues. It belongs to the class of Selective Progesterone Receptor Modulators (SPRM).

#### **MEETING OBJECTIVES:**

The objective of the meeting was to discuss the format and contents of the NDA file to support an NDA submission for ulipristal acetate in emergency contraception.

#### **DISCUSSION POINTS:**

The Sponsor's questions are presented below in *italics*, followed by the Division's responses that were provided to the sponsor on December 10, 2008, in normal text. Additional discussion held during the meeting is summarized below in **bold** text.

1. *Is this [to provide bioequivalence results for the products made by two manufacturers using different manufacturing processes during the review cycle] acceptable to the Agency?*

##### Division Response:

No, the application should be complete upon submission. Therefore, the results of the bioequivalence (BE) study to support the addition of the second manufacturing site cannot be submitted during the review cycle, but must be submitted in the original application.

As outlined in the Division's responses to the August 18, 2008, submission the Leon Farma batches should be submitted with a minimum of six months of stability data in the original application. Additional stability data will be accepted up to five months into the review cycle, but in order to meet the timelines in the *Good Review Management Practices (GRMP) Guidance*, the Division will not commit to review any additional stability data submitted after that time.

The Division has the following additional comments:

- A USAN designation should be used for the established name. It is not acceptable to use the International Nonproprietary Name (INN) designation for NDA approval.
- In the NDA submission, provide a comprehensive table/list of all facilities involved in production of the drug substance and drug product with full street address of the actual manufacturing and/or testing site (not the corporate office), contact information of an individual at the site, detailed responsibilities of that facility and a date of when the facility was last inspected by FDA.

This information will help to facilitate inspection requests. This comprehensive table should be attached to the 356h. Full information should still be provided in the appropriate sections of Modules 2 and 3.

- As stated in the information letter sent on October 17, 2008, in response to the August 18, 2008 correspondence, an *in vivo* bioequivalence study is required when the drug product is manufactured by two different manufacturers using different (b) (4). Results from the bioequivalence study should be submitted at the time of NDA submission; it is not acceptable to submit the study results during the review cycle.
- For each drug product used for all previous clinical studies, provide a table listing the study number, formulation number or identifier, formulation composition, manufacturer & manufacturing site(s), and differences in manufacturing process.

#### **Additional Discussion at the Meeting:**

**The Sponsor acknowledged the need to do a BE study if two manufacturing sites are to be used. The Sponsor requested to submit the BE study and information about the second manufacturing site three months into the review cycle; the Division reiterated that all data needed to be complete at the time of the initial submission. The Sponsor asked whether a BE study would still be needed if only the Leon Farma manufacturing site were included in the initial application. The Division stated that the BE data would still be needed to link the two sites, since the (b) (4) site manufactured the clinical trial materials.**

**The Sponsor inquired whether the proposed USAN designation would need to have been approved at the time of the initial submission. The USAN designation should be accepted by the time the NDA action is taken, but is not required for filing. The Sponsor should indicate in the submission that the USAN designation is under consideration. With this explanation, it will be acceptable to refer to the product in the NDA application under the INN designation.**

**The Division will respond to specific questions submitted to the IND about the requested facilities list. The Division is requesting identification of a contact person at each site involved in the application in order to facilitate inspection requests.**

**The Sponsor stated that the BE study will be performed with pilot scale batches from Leon Farma, comprising (b) (4). The Division stated that this will be sufficient as long as it represents at least 10% of the anticipated commercial batch size.**

2. *Does the Agency agree that the listed studies meet the nonclinical requirements for this NDA?*

Division Response:

The nonclinical program appears adequate to support a NDA. A complete review of all supporting safety data will be performed after filing.

3. *If this PPN study is not completed at time of application, does the Agency agree to receive results of this study during the review cycle?*

Division Response:

No, all necessary nonclinical studies to assess the safety of ulipristal in potentially pregnant women must be submitted with the original NDA submission.

**Additional Discussion at the Meeting:**

**The Sponsor agreed that the peri- and post-natal study will be provided in the NDA submission.**

4. *Does the Agency agree that the data analysis and presentation are appropriate for their review?*

Division Response:

As stated in the End of Phase 2 Meeting minutes sent on May 13, 2004, the Absorption, Distribution, Metabolism, and Elimination (ADME) and potential for drug-drug interactions should be characterized for CDB-2914. As this product is a new chemical entity, a mass balance study should be conducted to characterize the elimination pathway. At the time of NDA submission, address the ADME properties, mass balance of CDB-2914 and drug-drug interaction potential.

In order to utilize the efficacy data from the phase 2 studies in support of the NDA, an *in vivo* bioequivalence study with the 50 mg unmicronized capsules and the 30 mg micronized tablets may be required. In order to utilize the safety data from the phase 2 studies, relative bioavailability of the two formulations should be assessed.

For ease of review, provide a table listing all the clinical and clinical pharmacology studies with the corresponding dose, dosing regimen, number of subjects enrolled/completed, formulation number, and pharmacokinetics (PK) information (i.e.  $C_{max}$ ,  $T_{max}$ ,  $AUC_{0-t}$ ,  $AUC_{0-inf}$ , and  $t_{1/2}$ ).

The Division reminds the Sponsor of the following comment provided on August 10, 2007, following review of the amended protocol 2914-004:

The Division has not previously allowed exclusion from the efficacy analysis of pregnancies deemed “noncompatible” with emergency contraception failure.

The Division acknowledges the plan to conduct a secondary efficacy analysis including such subjects in the “mITT2” population, but the Division may consider this the appropriate primary analysis population.

**Additional Discussion at the Meeting:**

The Sponsor agreed to address ADME, mass balance and drug-drug interactions in the NDA submission. The formulation used in phase 2 is no longer available, so a direct BE study cannot be conducted to link the phase 2 and phase 3 formulations. The Sponsor suggested that plasma concentration data are available on both the phase 2 and phase 3 formulations, and should provide comparative exposure data to allow some reliance on safety data obtained in phase 2. Although different bioanalytical methods were used in the clinical trials, there is at least one trial that used both the RIA and LC/MS assays to measure drug concentration in the same clinical samples and that may provide a link between the assays. The Sponsor agreed to describe the different assays, and how they can be bridged, in the NDA submission. The summary table will also list the bioanalytical method used in each PK study.

The Sponsor clarified that in the mITT2 analysis, which includes “noncompatible” pregnancies, pre-treatment pregnancies (as determined by a positive high sensitivity urine pregnancy test done on Day 1, prior to dosing) will still be excluded. This is acceptable to the Division. However, the Division will make its own determination of which pregnancies should be included and therefore, requested that data listings be submitted for all pregnancies detected during the trial. The Sponsor further clarified that “noncompatible” pregnancies are those determined to have occurred outside the “fertility window” of the date of last unprotected intercourse + six days.

5. *Does the Agency agree that this proposal could serve as the basis for a Written Request for pediatric studies?*

**Division Response:**

The proposal submitted in the meeting package was not fully legible and provided only a synopsis of the proposed study, thus the Division cannot comment on the suitability of this proposal as the basis for a Written Request. However, the plan to enroll subjects from the age of 15 up does not appear to satisfy the Pediatric Research Equity Act, which requires studies in children from birth to age 16. While the Division would support a partial exemption for pediatric studies (for premenarchal females), the population of postmenarchal females would comprise adolescents younger than age 15. The Sponsor should propose a study that will address the full population of postmenarchal females. Refer to the September 2005 draft *Guidance for Industry, How to Comply with the Pediatric Research Equity Act*, available at <http://www.fda.gov/cder/guidance/6215dft.pdf>.

The “pediatric plan” (including deferral and exemption requests as well as any proposed studies) submitted in the NDA will be reviewed jointly by the Division and by the Pediatric Review Committee (PeRC).

**Additional Discussion at the Meeting:**

The Sponsor requested further clarification about the submission that would serve as the basis of a Written Request. If the NDA submission will request both a partial exemption and a deferral, the Sponsor must provide a proposed plan for pediatric development in the population for which they request the deferral. Included in this plan should be specific timeframes. The full protocol does not have to be provided in

**the initial NDA submission. A Written Request will be issued when an agreement between the Division and the Sponsor regarding the full protocol and the timeframes for completion is reached.**

6. *Does the Agency agree that the eCTD sample submission can be waived?*

Division Response:

Yes.

7. *Does the Agency agree with the proposed electronic formats and organization of the eCTD submissions?*

Division Response:

The proposed electronic format of the eCTD submission is acceptable if it conforms to the most recent FDA guidance available at <http://www.fda.gov/cder/regulatory/ersr/ectd.htm>.

Refer to the Study Data Specifications at

<http://www.fda.gov/cder/regulatory/ersr/Studydata.pdf> for preparing datasets.

The Division also requests safety data from all studies, including those using doses below or above 30 mg. Case Report Forms (CRFs) should also be submitted for all subjects who experience serious adverse events (SAEs), regardless of whether they discontinue the study, and for all subjects who discontinue due to any adverse event, not solely an SAE. Narratives should be provided for all subjects who experienced death, pregnancy, SAE or discontinuation due to an adverse event.

**Additional Discussion at the Meeting:**

**The Sponsor proposed to submit CRFs only for subjects who received ulipristal; this is acceptable to the Division.**

8. *Can the Agency confirm that this trade name is acceptable?*

Division Response:

The acceptability of the proposed trade name will be determined during the review of the NDA submission. Acceptability of a trade name during the IND stage is not considered a final determination.

**Additional Discussion at the Meeting:**

**The Sponsor asked whether lack of acceptability of a name could be communicated early in the review cycle, and whether it would be advisable to submit several name options. A recent Guidance for Industry, *Contents of a Complete Submission for the Evaluation of Proprietary Names*, November 2008, outlines the guidelines for such requests. The Sponsor can request a proprietary name review during the IND stage.**

**Additional Statistical Comments:**

- The efficacy dataset should include flags for all subjects who were repeat enrollers. These flags should indicate the repeat enrollment occurrence, for example, first time, second time, etc.
- The flow chart on page 168 of the briefing document states that 106 subjects were removed from the ITT Completers population due to "not known pregnancy status after EC intake." Provide additional primary efficacy sensitivity analyses including these subjects in the mITT, mITT2, and ITT Completers populations by categorizing them as treatment failures.

**Additional Discussion at the Meeting:**

The Sponsor requested to do a sensitivity analysis based on assigning the subset of subjects with unknown pregnancy status the pregnancy rate expected in the absence of any treatment effect, rather than treating them all as treatment failures, as was requested by the Division.

[Post-meeting comment: After consulting with the statistical reviewer, the Division continues to request the sensitivity analysis considering all "unknowns" as treatment failures. The Sponsor may also provide additional sensitivity analyses if desired.]

**Additional Topics Discussed at the Meeting:**

- The Division noted that the only approved progesterone receptor modulator, mifepristone, was approved for use as an abortifacient under restrictive conditions. Given that ulipristal may have similar abortifacient potential, the Sponsor should address in the NDA application how ulipristal can be safely made available under a more open plan, and how the Sponsor will guard against off-label use as an abortifacient. The Division inquired as to the relative abortifacient potency of ulipristal as compared to mifepristone; the Sponsor noted that of 29 on-treatment pregnancies, only six terminated spontaneously, and six were ongoing (the remainder terminated electively).
- Details of the effect of food were requested; the Sponsor indicated that taking ulipristal with food resulted in a statistically significant decrease in C<sub>max</sub> (about 40%), increased T<sub>max</sub> by about one hour, and caused a 20-25% increase in AUC. Overall, the Sponsor believes there will be no clinical impact of taking with food.

Linked Applications

Sponsor Name

Drug Name / Subject

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IND 49381

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Laboratoire HRA Pharma  
261 Madison Ave, 24th FL  
New York, NY 10016

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CDB-2914 (ulipristal acetate) tablets

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/s/

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LISA M SOULE  
02/26/2009



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

IND 49,381

HRA Pharma Laboratories  
Attention: Erin Gainer  
Director, Research and Development and Chief Executive Officer, HRA Pharma, LLC  
15 East 26<sup>th</sup> Street, Suite 1617  
New York, NY 10010

Dear Dr. Gainer:

Please refer to your Investigational New Drug (IND) application submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for CDB-2914.

We also refer to your submission dated June 16, 2006, requesting a Type A meeting to discuss the conclusions of the Special Protocol Assessment for Protocols 2914-004 and 2914-005.

We also refer to the meeting between representatives of your firm and the FDA on July 25, 2006.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, please call Nenita Crisostomo, R.N., Regulatory Health Project Manager, at (301) 796-2130.

Sincerely,

*(signature page)*

Lisa M. Soule, M.D.  
Medical Team Leader  
Division of Reproductive and Urologic  
Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

Enclosure

## MEMORANDUM OF MEETING MINUTES

**MEETING DATE:** July 25, 2006 **Time:** 2:30-4:00 PM

**Place:** Food and Drug Administration  
10903 New Hampshire Avenue, Building 22, Conf. Room 1313  
Silver Spring, MD 20903

**IND** 49,381

**Drug Name:** CDB-2914

**Indication:** Emergency Contraception

**Sponsor:** HRA Pharma Laboratories

**Type of Meeting:** Type A, Post-SPA

**Meeting Chair:** Lisa M. Soule, M.D.

**Meeting Recorder:** Eufrecina DeGuia

### **FDA Attendees:**

Scott Monroe, M.D. – Acting Director, Division of Reproductive and Urologic Products (DRUP)  
Lisa Soule, M.D. – Medical Team Leader, DRUP  
Ronald Orleans, M.D. – Medical Officer, DRUP  
Lisa Kammerman, Ph.D. – Team Leader, Statistician, Division of Biometrics II, Office of  
Translational Sciences  
Eufrecina DeGuia – Regulatory Health Project Manager, DRUP  
Jennifer Mercier – Chief, Project Management Staff, DRUP

### **HRA Pharma Attendees:**

Erin Gainer – Director, Research and Development, HRA Pharma; CEO, HRA Pharma, LLC  
Henri Mathe – Clinical Trial Coordinator, HRA Pharma  
Paul Fine, M.D. – Medical Director, Planned Parenthood Houston and SE Texas

**Background:** HRA Pharma submitted a Special Protocol Assessment Request for Protocols 2914-004 and 2914-005 to the Division on April 20, 2006. The Division provided responses to the Sponsor's questions and additional comments on the protocols on June 8, 2006. The meeting is requested to discuss the Division's recommendations about the two phase 3 safety and efficacy protocols.

**Objective:** The objective of the meeting is to reach agreement on the primary efficacy analysis, and the secondary objectives and corresponding analyses for both studies, the definition of study success in Protocol 2914-005, and the pooled analysis of the two studies.

## SPONSOR'S QUESTIONS AND DIVISION'S RESPONSES

**Question #1:** *Does the Agency agree with the proposed definitions (endpoint, population) and statistical methodology for the primary efficacy analysis of both studies?*

**Response:** The Division agrees with the proposed primary efficacy endpoint to be used in both studies:

- The pregnancy rate calculated as the number of subjects being pregnant after the intake of emergency contraception (EC), divided by the number of subjects having received EC.
- The pregnancy rate will be compared to the expected pregnancy rate in the absence of EC, estimated according to method provided by Trussell, et al (1998) and using pooled recognizable set of conception probabilities. Furthermore, in the event that a woman has had multiple acts of unprotected intercourse before treatment during the cycle, the conception probability taken into account will be that of the act of intercourse carrying the greatest conception probability.
- In the case where a subject is enrolled more than once, only the first participation will be used in the efficacy analysis.

Regarding the analysis populations, the Division considers the modified intent-to-treat (mITT) analysis to be primary. The Division is in agreement with use of a mITT population defined as all subjects who have been randomized and received EC, who have known pregnancy status following EC intake, and who do not have a pregnancy identified as starting prior to EC intake. However, the Sponsor should submit CRFs for all pregnancies, so that the Division can confirm the Data Safety Monitoring Board's (DSMB's) assessment of the timing of conception.

The populations used for efficacy calculations, both mITT and per protocol (PP), should include all women aged 35 or under. Discrepancies between results using the mITT and PP populations will be a review issue.

The Division agrees generally with the statistical methodology proposed; however, the Statistical Analysis Plan should be submitted for review by the Division prior to locking of the database. As the randomization in Study 2914-004 will be stratified by center and by time window of EC intake (up to 72 hours or from 72h to 120h), the Division recommends analyses which reflect this stratification.

### **Additional Statistical Comments:**

The Division requests that an ITT analysis be conducted, in addition to the mITT and PP analyses. It will be acceptable to exclude subjects from the ITT population who have no follow-up data on pregnancy; however, subjects who become pregnant should be included regardless of the timing of conception in regards to intake of EC.

**Question #2:** *Does the Agency agree with the proposed definition of success for Study 2914-005?*

**Response:** Yes, the Division agrees with the definition of success noted on page 5/32: the positive outcome of both:

- the primary efficacy analysis (demonstration that the upper bound of the 95% two-sided confidence interval around the point estimate of the observed pregnancy rate after taking CDB-2914 between 48 and 120 hours after unprotected intercourse is lower than the

expected pregnancy rate in the absence of EC, estimated by the Trussell method cited in Question 1), and

- the “secondary efficacy analysis” (demonstration that the upper bound of the 95% two-sided confidence interval around the point estimate of the observed pregnancy rate is lower than the clinical irrelevance threshold of 4%). The Division would consider this a co-primary endpoint, rather than a secondary endpoint.

**Additional discussion at the meeting:**

The Sponsor agreed that a two-sided 95% confidence interval would be used.

**Question #3: *Can the Agency provide feedback on the Sponsor’s modifications described in the below table and revised text provided in appendix?***

**Response:** The Division agrees with the majority of the Sponsor’s modifications described in the Table and in the Appendices. Several areas, however, warrant further comment:

1. Clarify the purpose of excluding subjects from Study 2914-005 who have unprotected intercourse within 48 hours of presentation. It is unclear in the Sponsor’s submission whether this exclusion applies to Study 2914-004 as well, as the policy is also referenced to Section I-C (Protocol 2914-004) on page 10/32.

**Additional discussion at the meeting:**

The Sponsor indicated that the exclusion of women presenting within 48 hours of unprotected intercourse will apply only to Study 2914-005, and is intended to allow a greater number of subjects in the 72-120 hour time window without necessitating an unduly large study. They concur with the Division’s concern that this might make recruiting difficult, as the majority of women in other trials have presented within 48 hours. The Sponsor has added additional centers, now up to 17 sites, to mitigate this.

2. Enrollment of a subset of subjects older than 35 years in both studies would be important to provide safety data in this age group, although the Division agrees that the primary efficacy data would be based upon women aged 35 or less.
3. The Division recommends that all repeat users of CDB-2914 in Study 2914-005 undergo safety laboratory testing, regardless of study site. The safety labs the Sponsor has agreed to incorporate in Study 2914-005 are not shown in the revised protocol.

**Additional discussion at the meeting:**

The Sponsor indicated that safety labs will be added to the protocol. The Sponsor agreed to obtain safety labs on all repeat users of CDB-2914 in Study 2914-005, not just at two sites. The Division agreed that random blood glucose sampling could be utilized, as it may not be possible to obtain a fasting glucose at baseline. The sample should be coded to indicate whether the sample was fasting or non-fasting. Specific labs to be obtained typically include complete blood count, chemistry, lipids, and liver function tests; additional labs are chosen based upon any signals noted in preclinical or early clinical development.

4. The regulatory purpose of the meta-analysis is not clear. The similarity of demographic characteristics of the two study populations should also be assessed before proceeding

with the analysis, in addition to assessing the homogeneity of the prevented fraction for each CDB-2914 group.

5. [REDACTED] (b) (4)

6. Clarify why concomitant use of glucocorticoids will be included as a cofactor in the planned logistic regression model used to estimate the pregnancy rate. Is such use expected to modify the efficacy of CDB-2914 or the underlying risk of pregnancy?

**Additional discussion at the meeting:**

The Sponsor plans to model the effect of glucocorticoid use, since CDB-2914 binds to the glucocorticoid receptor, although with less affinity than to the progesterone receptor. It is theoretically possible that concomitant use of glucocorticoids might alter the efficacy of CDB-2914. The Division asked that the logistic regression be run with and without this cofactor.

**Additional discussion at the meeting:**

The Sponsor sought clarification on the Division's invitation to seek another meeting to discuss the overall development plan. This would not be a Type A meeting, but could provide an opportunity to discuss the preclinical work in addition to the planned clinical studies. The Sponsor agreed to provide the Division with information about the preclinical program.

The Sponsor indicated that they plan to conduct Study 2914-004 in the U.K., but would like to conduct it under the IND. It is acceptable for them to submit a waiver form for FDA Form 1572.

[REDACTED] (b) (4)

**Action Item:** The meeting minutes will be forwarded to the Sponsor within 30 days.

Concurrence By:

*Lisa M. Soule*

Lisa M. Soule, M.D.  
Clinical Team Leader

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

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Lisa Soule  
8/18/2006 03:22:02 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

IND 49,381

National Institute of Child Health and Human Development  
Attention: Diana Blithe, Ph.D.  
6100 Executive Boulevard, Room 8B13  
Bethesda, MD 20892

Dear Dr. Blithe:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for CDB-2914.

We also refer to the End of Phase 2 meeting between representatives of your agency, HRA Pharma, and the FDA on April 19, 2004. The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Karen Kirchberg, N.P., Regulatory Project Manager, at (301) 827-4254.

Sincerely,

Scott Monroe, M.D.  
Medical Team Leader  
Division of Reproductive and Urologic Drug  
Products, HFD-580  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

Enclosure

## Meeting Minutes

**Date:** April 19, 2004

**Time:** 1:00 PM – 2:30 PM

**Location:** PKLN; Conference Room “C”

**IND:** 49,381      **Indication:** Emergency Contraception

**Drug Name:** CDB-2914

**Sponsor:** National Institutes of Health, National Institutes of Child Health and Human Development (NICHD) and HRA Pharma

**Meeting Type:** End of Phase 2

**Meeting Chair:** Scott Monroe, M.D. - Medical Team Leader, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)

**Meeting Recorder:** Karen Kirchberg, N.P. - Regulatory Project Manager, DRUDP (HFD-580)

### **FDA Attendees:**

Florence Houn, M.D. - Director, Office of Drug Evaluation III

Donna Griebel, M.D. - Deputy Director, DRUDP (HFD-580)

Scott Monroe, M.D. - Medical Team Leader, DRUDP (HFD-580)

Ronald Orleans, M.D. - Medical Officer, DRUDP (HFD-580)

Dan Davis, M.D. - Medical Officer, DRUDP (HFD-580)

Ameeta Parekh, Ph.D. - Pharmacokinetics Team Leader, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)

Myong-Jin Kim, Pharm.D. - Pharmacokinetics Reviewer, OCPB @ DRUDP (HFD-580)

Lynnda Reid, Ph.D. - Pharmacology Supervisor, DRUDP (HFD-580)

Suzanne Thornton, Ph.D. - Pharmacology Reviewer, DRUDP (HFD-580)

Karen Kirchberg, N.P. - Regulatory Project Manager, DRUDP (HFD-580)

### **External Attendees:**

Diana Blithe, Ph.D. - Project Officer, CRHB, NICHD, NIH

Robert Spirtas, Dr.P.H. - Chief, CRHB, NICHD, NIH

Lynnette Nieman, M.D. - Senior Investigator, PREB, NICHD, NIH

Clinton Dart - Biometrics Manager, Health Decisions

André Ulmann, M.D., Ph.D. - CEO and Medical Director, HRA Pharma

Erin Gainer, M.P.H. - Head of Research and Development, HRA Pharma

**Background:** The drug, CDB-2914, is a selective progesterone receptor modulator being developed for use as emergency contraception.

## Sponsor's Questions and FDA's Answers and Comments

### Sponsor's Question:

1. When Phase 2 clinical study was initiated in 1998, no levonorgestrel emergency contraceptive product had been registered in the US. There were two industrial contenders at (b) (4) but only one of the two products was made available to us (b) (4). Unfortunately, this product has still not been registered in the US. We propose to use comparative *in vitro* dissolution tests to bridge the two formulations – would this be sufficient? If not, what additional data would be necessary?

### FDA Answer:

- If you intend to use the efficacy comparative data of CDB-2914 to the (b) (4) levonorgestrel product to support the approval of your product, using *in vitro* dissolution test comparison to bridge the two levonorgestrel formulations is not acceptable. A bioequivalence study should be conducted.

### Sponsor's Question

2. We anticipate that data from the ongoing pharmacokinetic comparison will be sufficient to allow rational selection of a micronized dose using Phase 1 and 2 clinical data generated with both micronized and unmicronized formulations. Once the appropriate dose of the micronized formulation has been selected, we propose to establish equivalence with respect to bioavailability using the protocol described in Appendix 2. Assuming equivalence (conventional bioequivalence range of 80% to 125%, n=18) of the selected micronized dose to the 50 mg unmicronized dose, would this permit utilization of the data from the Phase 2 studies?

### FDA Answer:

- This is acceptable.
- General Comments:
  - You should conduct a food effect study using the to-be-marketed formulation. In addition, ADME of CDB 2914 and any drug-drug interaction potential should be characterized. Given that CDB-2914 is a new chemical entity, a mass balance study should be conducted to characterize the elimination pathway(s). If a specific ethnic group is allocated to any age group during the clinical trial(s), a bridging study may need to be conducted in order to extrapolate the clinical data to the general population (E5; Guidance on Ethnic Factors in the Acceptability of Foreign Clinical Data).
  - We also recommend that you submit the data from 02-CH-0219 (PK study of 3 preparations of CDB-2914) and 2914-003 (BE study of 50 mg capsule and xx mg micronized tablet) before your Phase 3 study is initiated.

### Sponsor's Question

3. With this intermediate dose of micronized drug, we plan to conduct a confirmatory Phase 3 study. Because the large-scale Phase 2 study involved comparison with a reference product, we propose a multicenter international open-label study design with a well-defined statistical endpoint.
  - a. Would such a design be acceptable for the pivotal study in the NDA?

**FDA Answer:**

- We prefer that you conduct a comparative study against an approved drug for emergency contraception (e.g., Plan B). This study could have either a superiority or non-inferiority endpoint.
- Alternatively, you can conduct a non-comparative clinical trial based on a mutually agreed to point estimate of efficacy and 95% confidence interval. However, because of differences in your proposed study design as well as possible differences in the fecundity rate in your study population compared to previous studies, there is a risk that treatment with your drug would not achieve the agreed to efficacy endpoint. Inclusion of an approved comparator would provide protection against such an outcome if your drug was truly as effective as Plan B.

**Sponsor's Question**

- b. In the context of a multicenter international study, what proportion of patients would need to be included in US centers?

**FDA Answer:**

- We prefer that at least 50% of the patients be from US centers.

**Sponsor's Question**

- c. Our efficacy calculation is based on patients enrolled within 72 hours of unprotected intercourse. However, based on pharmacodynamic data we would like to enroll patients up to 120 hours. Is the current design appropriate?

**FDA Answer:**

- Yes, but a sufficient number of subjects enrolled within 72 hours of intercourse would be required for you to demonstrate non-inferiority or superiority if you conduct a comparative trial or to achieve an acceptable 95% confidence interval around the point estimate if you conduct a non-comparative trial.

**Additional Comments:****Toxicology**

- Submit a list of all pharmacology/toxicology studies which have been conducted and indicate the drug form (unmicronized or micronized).
- Provide the serial number of the submission for the final study report if already submitted or submit the final study report for the monkey study in which the micronized drug was administered and shown to have higher bioavailability than the unmicronized drug.

**Clinical**

- For a new molecular drug product (e.g., CDB-2914), 2 adequate and well-controlled clinical trials are generally required to support a NDA. If you are able to demonstrate that (a) the levonorgestrel drug product used in Study CCN002 is bioequivalent to Plan B and (b) the gelatin capsule formulation of CDB-2914 is bioequivalent to the to-be-marketed drug product, Study CCN002 might qualify as 1 of the 2 adequate and well controlled clinical trials. However, we will need to review the data and final report for Study CCN002 before we can determine if it would qualify as 1 of 2 adequate and well controlled clinical trials.
- We suggest that you submit all clinical protocols to the Division for review prior to initiating the respective clinical trial.

**Issues Requiring Further Discussion:**

- Sponsor requested clarification regarding mass balance question for a single dose preparation.

**Action:**

- Meeting minutes to sponsor in 30 days

Minutes prepared: K. Kirchberg, N.P.

Minutes concurred: S. Monroe, M.D.

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

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Scott Monroe  
5/13/04 05:34:42 PM

# ACTION PACKAGE CHECKLIST

## APPLICATION INFORMATION<sup>1</sup>

|  |                               |  |
|--|-------------------------------|--|
| NDA # 022474<br>BLA #  | NDA Supplement #<br>BLA STN # | If NDA, Efficacy Supplement Type:  |
| Proprietary Name: Ella<br>Established/Proper Name: ulipristal acetate<br>Dosage Form: 30 mg tablet   |                               | Applicant: Laboratoire HRA Pharma<br>Agent for Applicant (if applicable): Target Health  |
| RPM: Pamela Lucarelli  |                               | Division: Division of Reproductive and Urologic Products (DRUP)  |
| <p>NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>(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). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)</p> |                               | <p><u>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</u><br/>Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p>If no listed drug, explain.</p> <p><input type="checkbox"/> This application relies on literature.<br/> <input type="checkbox"/> This application relies on a final OTC monograph.<br/> <input type="checkbox"/> Other (explain)</p> <p><b><u>Two months prior to each action, review the information in the 505(b)(2) Assessment and submit the draft to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</u></b></p> <p><b><u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u></b></p> <p><input type="checkbox"/> No changes    <input type="checkbox"/> Updated    Date of check:</p> <p><b>If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</b></p> |
| ❖ Actions  |                               |  |
| <ul style="list-style-type: none"> <li>• Proposed action</li> <li>• User Fee Goal Date is <u>August 13, 2010</u></li> </ul>  |                               | <input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR   |
| <ul style="list-style-type: none"> <li>• Previous actions (<i>specify type and date for each action taken</i>)</li> </ul>  |                               | <input checked="" type="checkbox"/> None   |

<sup>1</sup> The **Application Information** section is (only) a checklist. The **Contents of Action Package** section (beginning on page 5) lists the documents to be included in the Action Package.

|  |  |
|--|--|
| <p>❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received?<br/>         Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see <a href="http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf">http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf</a>). If not submitted, explain _____</p>   | <p><input type="checkbox"/> Received</p>   |
| <p>❖ Application Characteristics <sup>2</sup></p>  |  |
| <p>Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority<br/>         Chemical classification (new NDAs only): 1</p> <p><input type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch<br/> <input type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch<br/> <input type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC</p> <p>NDAs: Subpart H <span style="margin-left: 200px;">BLAs: Subpart E</span><br/> <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <span style="margin-left: 100px;"><input type="checkbox"/> Accelerated approval (21 CFR 601.41)</span><br/> <input type="checkbox"/> Restricted distribution (21 CFR 314.520) <span style="margin-left: 100px;"><input type="checkbox"/> Restricted distribution (21 CFR 601.42)</span></p> <p>Subpart I <span style="margin-left: 200px;">Subpart H</span><br/> <input type="checkbox"/> Approval based on animal studies <span style="margin-left: 100px;"><input type="checkbox"/> Approval based on animal studies</span></p> <p><input type="checkbox"/> Submitted in response to a PMR<br/> <input type="checkbox"/> Submitted in response to a PMC<br/> <input type="checkbox"/> Submitted in response to a Pediatric Written Request</p> <p>Comments:</p> |  |
| <p>BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)</p>  | <p><input type="checkbox"/> Yes, dates</p>   |
| <p>❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)</p>  | <p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>  |
| <p>❖ Public communications (<i>approvals only</i>)</p>   |  |
| <ul style="list-style-type: none"> <li>• Office of Executive Programs (OEP) liaison has been notified of action</li> </ul>   | <p><input checked="" type="checkbox"/> Yes <input type="checkbox"/> No</p>   |
| <ul style="list-style-type: none"> <li>• Press Office notified of action (by OEP)</li> </ul>   | <p><input checked="" type="checkbox"/> Yes <input type="checkbox"/> No</p>   |
| <ul style="list-style-type: none"> <li>• Indicate what types (if any) of information dissemination are anticipated</li> </ul>  | <p><input type="checkbox"/> None<br/> <input checked="" type="checkbox"/> HHS Press Release<br/> <input type="checkbox"/> FDA Talk Paper<br/> <input type="checkbox"/> CDER Q&amp;As<br/> <input type="checkbox"/> Other</p> |

<sup>2</sup> Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

|  |   |
|--|---|
| ❖ Exclusivity  |   |
| <ul style="list-style-type: none"> <li>Is approval of this application blocked by any type of exclusivity?</li> </ul>  | <input checked="" type="checkbox"/> No <input type="checkbox"/> Yes   |
| <ul style="list-style-type: none"> <li>NDA and BLAs: Is there existing orphan drug exclusivity for the “same” drug or biologic for the proposed indication(s)? <i>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.</i></li> </ul>  | <input checked="" type="checkbox"/> No <input type="checkbox"/> Yes<br>If, yes, NDA/BLA # _____ and date exclusivity expires: _____                       |
| <ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>  | <input type="checkbox"/> No <input type="checkbox"/> Yes<br>If yes, NDA # _____ and date exclusivity expires: _____                                       |
| <ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>  | <input type="checkbox"/> No <input type="checkbox"/> Yes<br>If yes, NDA # _____ and date exclusivity expires: _____                                       |
| <ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>   | <input type="checkbox"/> No <input type="checkbox"/> Yes<br>If yes, NDA # _____ and date exclusivity expires: _____                                       |
| <ul style="list-style-type: none"> <li>NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>  | <input checked="" type="checkbox"/> No <input type="checkbox"/> Yes<br>If yes, NDA # _____ and date 10-year limitation expires: _____                     |
| ❖ Patent Information (NDAs only)   |   |
| <ul style="list-style-type: none"> <li>Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.</li> </ul>  | <input checked="" type="checkbox"/> Verified<br><input type="checkbox"/> Not applicable because drug is an old antibiotic.                                |
| <ul style="list-style-type: none"> <li>Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.</li> </ul>   | 21 CFR 314.50(i)(1)(i)(A)<br><input type="checkbox"/> Verified<br><br>21 CFR 314.50(i)(1)<br><input type="checkbox"/> (ii) <input type="checkbox"/> (iii) |
| <ul style="list-style-type: none"> <li>[505(b)(2) applications] If the application includes a <b>paragraph III</b> certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).</li> </ul>   | <input type="checkbox"/> No paragraph III certification<br>Date patent will expire _____  |
| <ul style="list-style-type: none"> <li>[505(b)(2) applications] For <b>each paragraph IV</b> certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark “N/A” and skip to the next section below (Summary Reviews)).</i></li> </ul> | <input type="checkbox"/> N/A (no paragraph IV certification)<br><input type="checkbox"/> Verified   |

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

Answer the following questions for **each** paragraph IV certification:

- (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?

Yes       No

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, 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 the rest of the patent questions.

If "**No**," continue with question (3).

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes       No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) 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 section below (Summary Reviews).

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

|   |  |
|---|--|
| <p>(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) 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).</p> <p><i>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 section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i></p> | <p><input type="checkbox"/> Yes    <input type="checkbox"/> No</p> |
| <p><b>CONTENTS OF ACTION PACKAGE</b></p>  |  |
| <p>❖ Copy of this Action Package Checklist<sup>3</sup></p>  | <p><input checked="" type="checkbox"/> Included</p>                |
| <p><b>Officer/Employee List</b></p>   |  |
| <p>❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)</p>  | <p><input checked="" type="checkbox"/> Included</p>                |
| <p>Documentation of consent/non-consent by officers/employees</p>   | <p><input checked="" type="checkbox"/> Included</p>                |
| <p><b>Action Letters</b></p>  |  |
| <p>❖ Copies of all action letters (<i>including approval letter with final labeling</i>)</p>  | <p>Action(s) and date(s) Approved<br/>August 13, 2010</p>          |
| <p><b>Labeling</b></p>  |  |
| <p>❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)</p>   |  |
| <ul style="list-style-type: none"> <li>• Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.</li> </ul>  | <p><input checked="" type="checkbox"/> Included Final PI</p>       |
| <ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>  | <p><input checked="" type="checkbox"/> Included</p>                |
| <ul style="list-style-type: none"> <li>• Example of class labeling, if applicable</li> </ul>  |  |

<sup>3</sup> Fill in blanks with dates of reviews, letters, etc.  
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|   |   |
|---|---|
| Medication Guide/Patient Package Insert/Instructions for Use ( <i>write submission/communication date at upper right of first page of each piece</i> )  | <input type="checkbox"/> Medication Guide<br><input checked="" type="checkbox"/> Patient Package Insert<br><input type="checkbox"/> Instructions for Use<br><input type="checkbox"/> None   |
| <ul style="list-style-type: none"> <li>Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.</li> </ul>  | <input checked="" type="checkbox"/> Included Final PPI  |
| <ul style="list-style-type: none"> <li>Original applicant-proposed labeling</li> </ul>  | <input checked="" type="checkbox"/> Included  |
| <ul style="list-style-type: none"> <li>Example of class labeling, if applicable</li> </ul>  |   |
| ❖ Labels ( <b>full color</b> carton and immediate-container labels) ( <i>write submission/communication date on upper right of first page of each submission</i> )  |   |
| <ul style="list-style-type: none"> <li>Most-recent draft labeling</li> </ul>  | <input checked="" type="checkbox"/> Included Original and Final   |
| ❖ Proprietary Name <ul style="list-style-type: none"> <li>Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>)</li> <li>Review(s) (<i>indicate date(s)</i>)</li> </ul>   | Ella -- January 25, 2010,<br>August 2, 2010   |
| ❖ Labeling reviews ( <i>indicate dates of reviews and meetings</i> )  | <input type="checkbox"/> RPM<br><input checked="" type="checkbox"/> DMEPA March 18, 2010,<br>July 9, 2010<br><input checked="" type="checkbox"/> DRISK July 28, 2010<br><input checked="" type="checkbox"/> DDMAC August 10, 2010<br><input type="checkbox"/> CSS<br><input checked="" type="checkbox"/> Other reviews SEALD<br>August 9, 2010, August 12, 2010 |
| <b>Administrative / Regulatory Documents</b>  |   |
| ❖ Administrative Reviews ( <i>e.g., RPM Filing Review<sup>4</sup>/Memo of Filing Meeting</i> ) ( <i>indicate date of each review</i> )  | <input checked="" type="checkbox"/> Included December 12, 2010  |
| ❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte   | <input checked="" type="checkbox"/> Not a (b)(2)  |
| ❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment ( <i>indicate date</i> )  | <input checked="" type="checkbox"/> Not a (b)(2)  |
| ❖ NDAs only: Exclusivity Summary ( <i>signed by Division Director</i> )   | <input checked="" type="checkbox"/> Included  |
| ❖ Application Integrity Policy (AIP) Status and Related Documents<br><a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a>  |   |
| <ul style="list-style-type: none"> <li>Applicant is on the AIP</li> </ul>   | <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No   |
| <ul style="list-style-type: none"> <li>This application is on the AIP               <ul style="list-style-type: none"> <li>If yes, Center Director's Exception for Review memo (<i>indicate date</i>)</li> <li>If yes, OC clearance for approval (<i>indicate date of clearance communication</i>)</li> </ul> </li> </ul> | <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No<br><br><input type="checkbox"/> Not an AP action  |
| ❖ Pediatrics ( <i>approvals only</i> ) <ul style="list-style-type: none"> <li>Date reviewed by PeRC <u>June 30, 2010</u><br/>If PeRC review not necessary, explain: _____</li> <li>Pediatric Page (<i>approvals only, must be reviewed by PERC before finalized</i>)</li> </ul>   | <input checked="" type="checkbox"/> Included  |
| ❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent ( <i>include certification</i> )   | <input checked="" type="checkbox"/> Verified, statement is acceptable   |
| ❖ Outgoing communications ( <i>letters (except action letters), emails, faxes, telecons</i> )   | <input checked="" type="checkbox"/> Included  |

<sup>4</sup> Filing reviews for scientific disciplines should be filed behind the respective discipline tab.  
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|  |   |
|--|---|
| ❖ Internal memoranda, telecons, etc.   | <input checked="" type="checkbox"/> Included                            |
| ❖ Minutes of Meetings  |   |
| • Regulatory Briefing ( <i>indicate date of mtg</i> )  | <input checked="" type="checkbox"/> No mtg                              |
| • If not the first review cycle, any end-of-review meeting ( <i>indicate date of mtg</i> )   | <input checked="" type="checkbox"/> N/A or no mtg                       |
| • Pre-NDA/BLA meeting ( <i>indicate date of mtg</i> )  | <input type="checkbox"/> No mtg December 12, 2008                       |
| • EOP2 meeting ( <i>indicate date of mtg</i> )   | <input type="checkbox"/> No mtg April 19, 2004                          |
| • Other milestone meetings (e.g., EOP2a, CMC pilots) ( <i>indicate dates of mtgs</i> )   | <input checked="" type="checkbox"/> Included SPA July 25, 2006          |
| ❖ Advisory Committee Meeting(s)  | <input type="checkbox"/> No AC meeting                                  |
| • Date(s) of Meeting(s)  | June 17, 2010   |
| • 48-hour alert or minutes, if available ( <i>do not include transcript</i> )  | <input checked="" type="checkbox"/> Included                            |
| <b>Decisional and Summary Memos</b>  |   |
| ❖ Office Director Decisional Memo ( <i>indicate date for each review</i> )   | <input type="checkbox"/> None August 13, 2010                           |
| Division Director Summary Review ( <i>indicate date for each review</i> )  | <input type="checkbox"/> None August 13, 2010                           |
| Cross-Discipline Team Leader Review ( <i>indicate date for each review</i> )   | <input type="checkbox"/> None August 13, 2010                           |
| PMR/PMC Development Templates ( <i>indicate total number</i> )   | <input type="checkbox"/> None August 13, 2010 (5)                       |
| <b>Clinical Information<sup>5</sup></b>  |   |
| ❖ Clinical Reviews   |   |
| • Clinical Team Leader Review(s) ( <i>indicate date for each review</i> )  | See CDTL Review   |
| • Clinical review(s) ( <i>indicate date for each review</i> )  | August 6, 2010  |
| • Social scientist review(s) (if OTC drug) ( <i>indicate date for each review</i> )  | <input checked="" type="checkbox"/> None                                |
| ❖ Financial Disclosure reviews(s) or location/date if addressed in another review<br>OR<br>If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not ( <i>indicate date of review/memo</i> ) | <input checked="" type="checkbox"/> Included in Clinical Review Page 12 |
| ❖ Clinical reviews from immunology and other clinical areas/divisions/Centers ( <i>indicate date of each review</i> )  | <input type="checkbox"/> None OSE August 2, 2010                        |
| ❖ Controlled Substance Staff review(s) and Scheduling Recommendation ( <i>indicate date of each review</i> )   | <input checked="" type="checkbox"/> Not applicable                      |
| ❖ Risk Management  |   |
| • REMS Documents and Supporting Statement ( <i>indicate date(s) of submission(s)</i> )   |   |
| • REMS Memo(s) and letter(s) ( <i>indicate date(s)</i> )   |   |
| • Risk management review(s) and recommendations (including those by OSE and CSS) ( <i>indicate date of each review and indicate location/date if incorporated into another review</i> )  | <input checked="" type="checkbox"/> None                                |
| ❖ DSI Clinical Inspection Review Summary(ies) ( <i>include copies of DSI letters to investigators</i> )  | <input type="checkbox"/> None requested 4 sites include                 |

<sup>5</sup> Filing reviews should be filed with the discipline reviews.  
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|  |   |
|--|---|
| <b>Clinical Microbiology</b> <input checked="" type="checkbox"/> None  |   |
| Clinical Microbiology Team Leader Review(s) (indicate date for each review)  | <input type="checkbox"/> None   |
| Clinical Microbiology Review(s) (indicate date for each review)  | <input type="checkbox"/> None   |
| <b>Biostatistics</b> <input type="checkbox"/> None   |   |
| ❖ Statistical Division Director Review(s) (indicate date for each review)  | <input checked="" type="checkbox"/> None  |
| Statistical Team Leader Review(s) (indicate date for each review)  | <input checked="" type="checkbox"/> None  |
| Statistical Review(s) (indicate date for each review)  | <input type="checkbox"/> None December 15, 2009,<br>July 22, 2010                         |
| <b>Clinical Pharmacology</b> <input type="checkbox"/> None   |   |
| ❖ Clinical Pharmacology Division Director Review(s) (indicate date for each review)  | <input checked="" type="checkbox"/> None  |
| Clinical Pharmacology Team Leader Review(s) (indicate date for each review)  | <input checked="" type="checkbox"/> None  |
| Clinical Pharmacology review(s) (indicate date for each review)  | <input type="checkbox"/> None December 4, 2009,<br>July 9 and 23 2010,<br>August 12, 2010 |
| ❖ DSI Clinical Pharmacology Inspection Review Summary (include copies of DSI letters)  | <input checked="" type="checkbox"/> None  |
| <b>Nonclinical</b> <input type="checkbox"/> None   |   |
| ❖ Pharmacology/Toxicology Discipline Reviews   |   |
| • ADP/T Review(s) (indicate date for each review)  | <input type="checkbox"/> None July 29, 2010   |
| • Supervisory Review(s) (indicate date for each review)  | <input type="checkbox"/> None August 11, 2010   |
| • Pharm/tox review(s), including referenced IND reviews (indicate date for each review)  | <input type="checkbox"/> None November 25, 2009,<br>June 28, 2010, August 13, 2010        |
| ❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (indicate date for each review)                         | <input checked="" type="checkbox"/> None  |
| ❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)   | <input checked="" type="checkbox"/> No carc   |
| ❖ ECAC/CAC report/memo of meeting  | <input checked="" type="checkbox"/> None  |
| ❖ DSI Nonclinical Inspection Review Summary (include copies of DSI letters)  | <input checked="" type="checkbox"/> None requested  |
| <b>Product Quality</b> <input type="checkbox"/> None   |   |
| ❖ Product Quality Discipline Reviews   |   |
| • ONDQA/OBP Division Director Review(s) (indicate date for each review)  | <input type="checkbox"/> None August 12, 2010   |
| • Branch Chief/Team Leader Review(s) (indicate date for each review)   | <input checked="" type="checkbox"/> None  |
| • Product quality review(s) including ONDQA biopharmaceutics reviews (indicate date for each review)                                 | <input type="checkbox"/> None December 4, 2009<br>June 25, 2010, August 12, 2010          |
| ❖ Microbiology Reviews   | <input checked="" type="checkbox"/> Not needed  |
| <input type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) (indicate date of each review)             |   |
| <input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (DMPQ/MAPCB/BMT) (indicate date of each review) |   |
| ❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer (indicate date of each review)                    | <input type="checkbox"/> None Biopharmaceutics<br>Review Included                         |

|   |   |
|---|---|
| ❖ Environmental Assessment (check one) (original and supplemental applications)   |   |
| <input checked="" type="checkbox"/> Categorical Exclusion ( <i>indicate review date</i> )( <i>all original applications and all efficacy supplements that could increase the patient population</i> )   | See Product Quality June 25, 2010 Page 51   |
| <input type="checkbox"/> Review & FONSI ( <i>indicate date of review</i> )  |   |
| <input type="checkbox"/> Review & Environmental Impact Statement ( <i>indicate date of each review</i> )  |   |
| ❖ Facilities Review/Inspection  |   |
| <input type="checkbox"/> NDAs: Facilities inspections (include EER printout) ( <i>date completed must be within 2 years of action date</i> ) ( <i>only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites<sup>o</sup></i> ) | Date completed: May 10, 2010<br><input checked="" type="checkbox"/> Acceptable<br><input type="checkbox"/> Withhold recommendation<br><input type="checkbox"/> Not applicable         |
| <input type="checkbox"/> BLAs: TB-EER ( <i>date of most recent TB-EER must be within 30 days of action date</i> ) ( <i>original and supplemental BLAs</i> )   | Date completed:<br><input type="checkbox"/> Acceptable<br><input type="checkbox"/> Withhold recommendation  |
| ❖ NDAs: Methods Validation ( <i>check box only, do not include documents</i> )  | <input type="checkbox"/> Completed<br><input type="checkbox"/> Requested<br><input type="checkbox"/> Not yet requested<br><input checked="" type="checkbox"/> Not needed (per review) |

<sup>o</sup> I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

## Appendix to Action Package Checklist

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

- (1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
- (2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
- (3) **Or** 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.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy 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).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
- (2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
- (3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
- (2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
- (3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's ADRA.