CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203159Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 203159 SUPPL # HFD #

Trade Name Skyla IUS

Generic Name levonorgestrel-releasing

Applicant Name Bayer Healthcare Pharmaceuticals, Inc.

Approval Date, If Known January 9, 2013

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:

N/A

d) Did the applicant request exclusivity?

YES ☒ NO ☐

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

3 years

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?

N/A

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# 21225 Mirena

NDA# 19897 Norplant

NDA# 21045 Plan B

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:

Study A52238, Protocol 310442
Study A46796, Protocol 308901

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

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

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

Investigation #1 YES ☐ NO ☒

Investigation #2 YES ☐ NO ☒

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

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

Investigation #1 YES ☐ NO ☒

Investigation #2 YES ☐ NO ☒

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

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

Study A52238, Protocol 310442
Study A46796, Protocol 308901

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

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

Investigation #1		!
		!
IND # 73505	YES ☒	! NO ☐
		! Explain:

Investigation #2		!
		!
IND # 73505	YES ☒	! NO ☐
		! Explain:

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

Investigation #1	!
	!
YES ☐	! 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:

==========

Name of person completing form: Charlene Williamson
Title: Regulatory Project Manager
Date: December 14, 2012

Name of Office/Division Director signing form: Audrey Gassman, M.D.
Title: Deputy Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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/s/

ZETA-MAE C WILLIAMSON
01/09/2013

AUDREY L GASSMAN
01/09/2013

From: Jo-Ann Ruane [jo-ann.ruane@bayer.com]
Sent: Friday, December 21, 2012 2:31 PM
To: Williamson, Charlene
Cc: Sharon Brown
Subject: RE: Information Request: Subject 244119

Dear Charlene,

The following information is provided in response to the 19 Dec 2012 FDA Information Request re: Subject 244119:

FDA Comment

The data is unclear regarding Subject 244119. There is a statement in the submission that the site made several attempts to contact this woman but was not successful. It goes on to say the woman was contacted on March 10, 2009 regarding a possible pregnancy. Please clarify this discrepancy. Was the subject indeed contacted? If she was not contacted, how was the pregnancy information obtained? If she was contacted, who contacted her and what information was obtained? If this subject was pregnant, what information do you have regarding last menstrual period, conception date and delivery date?

Bayer Response

The subject had LCS12 inserted on 27 Mar 2008 and she prematurely discontinued the study on 14 Nov 2008 due to the AE, post-coital bleeding. At the end of study visit (14 Nov 2008), a supervised in-office, high-sensitivity urine pregnancy test* was obtained and negative, and an ultrasound exam prior to removal of LCS12 demonstrated that it was in the correct location in situ. A narrative for this subject is available in the study report (module 5.3.5.2 A52238, page 1422 in report section 15). The subject was contacted by telephone successfully on 10 March 2009 as a routine, 3-month post-study call to ascertain whether or not a pregnancy had occurred. During that call, the subject reported that she had taken a home pregnancy test and that it was positive, but she did not provide (or the site did not record) the date of the home pregnancy test. No information was obtained at that time regarding the date of the last menstrual period, estimated conception date, or estimated date of confinement. Several subsequent attempts to contact the subject by telephone were unsuccessful. A certified letter was sent to the subject on 10 Feb 2010. The certified letter was returned to the site on 28 March 2010 (notation: unable to forward), and no further information has since been obtained.

*Note: The subject narrative incorrectly refers to a serum pregnancy test.

Would you confirm receipt of this email message? As always, please do not hesitate to contact me if you have any further questions.

Best regards,
Jo-Ann

_____

Jo-Ann Ruane
Global Regulatory Affairs
Bayer HealthCare Pharmaceuticals, Inc.
Office Phone: 973-487-2343
(b) (6)
Fax: 973-487-2016
e-mail: jo-ann.ruane@bayer.com

From: Williamson, Charlene [mailto:Charlene.Williamson@fda.hhs.gov]
Sent: Wednesday, December 19, 2012 11:25 AM
To: Williamson, Charlene; Jo-Ann Ruane
Subject: RE: Information Request: Subject 244119

Jo-Ann,

Please respond to this request within 7 days.

Thanks

Charlene

_____

From: Williamson, Charlene

Sent: Wednesday, December 19, 2012 11:07 AM

To: Jo-Ann Ruane

Cc: Williamson, Charlene

Subject: Information Request: Subject 244119

Jo-Ann,

Please review the below information request regarding Subject 244119.

Please acknowledge receipt of this email.

Charlene

The data is unclear regarding Subject 244119. There is a statement in the submission that the site made several attempts to contact this woman but was not successful. It goes on to say the woman was contacted on March 10, 2009 regarding a possible pregnancy. Please clarify this discrepancy. Was the subject indeed contacted? If she was not contacted, how was the pregnancy information obtained? If she was contacted, who contacted her and what information was obtained? If this subject was pregnant, what information do you have regarding last menstrual period, conception date and delivery date?

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/s/

ZETA-MAE C WILLIAMSON
12/21/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 203159

GENERAL ADVICE

Bayer Healthcare Pharmaceuticals, Inc.
Attention: Jo-Ann Ruane
Associate Director, Global Regulatory Affairs
P.O. Box 1000
Montville, NJ 07045-1000

Dear Ms. Ruane:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Skyla (Levonorgestrel-containing Intrauterine System) 13.5 mg.

We also refer to your November 9, 2012, submission, containing revised Primary Package container labeling, Secondary Carton labeling, and Patient Booklet Cover labeling.

We have reviewed the referenced material and have the following comments:

General Comments on Primary Package Container Label, Secondary Carton Labeling, and Patient Booklet Cover Labeling

- Ensure the established name is at least ½ the size of the proprietary name, taking into account all pertinent factors including typography, layout, contrast, and other printing features [21 CFR 201.10(g)(2)].

If you have any questions, call me at (301) 796-1025.

Sincerely,

{See appended electronic signature page}

Z. Charlene Williamson
Regulatory Health Project Manager
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

ZETA-MAE C WILLIAMSON
11/28/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 203159 **INFORMATION REQUEST**

Bayer HealthCare Pharmaceuticals Inc.
Attention: Jo-Ann Ruane, Associate Director, Global Regulatory Affairs
PO Box 1000
Montville, NJ 07045-1000

Dear Ms. Ruane:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the LCS12 intrauterine device.

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

In the Inserter Administration Device for LNG-IUS 13.5 mg Stability Report (preliminary) G.05.01630-01, you describe the testing conducted to support the functionality of the inserter over time. This report lacks important details that are necessary for determining the adequacy of the testing that was conducted. Please address the following:

- In section 2. Description and batch information, you indicate that one batch (C11040) was used for the testing. FDA typically requests testing on multiple lots because of the potential variability in devices across lots. Please either repeat your stability testing using samples obtained from different lots or provide a justification for why you do not believe it is necessary.

- In section 3. Storage conditions and testing times, a sample size of 10 is indicated. Please indicate whether 10 different samples were tested at each time point or whether a total of 10 samples were tested. In addition, please justify your sample size.

- As part of the storage conditions, you have described two different temperatures. Please indicate whether you used either or both of the stated conditions to accelerate the aging of the device. If so, please provide details on the accelerated aging protocol used. For additional information on the necessary type of information, you may refer to ASTM F1980-07 Standard Guide for Accelerated Aging of Sterile Barrier Systems for Medical Devices. In addition, you will need to conduct testing on real time aged samples to confirm the results of the accelerated aging tests.

- In section 4. Tested Parameter, you identify one tested functionality parameter. No other parameters were identified. Since the purpose of the testing should be to confirm that

there has been no deleterious affect of the aging on the device, an evaluation of the same parameters used for lot release are typically applied. Please either repeat this testing using all the testing applied at the time of lot release or justify why these tests are not necessary.

If you have any questions, call Kerri-Ann Jennings, Regulatory Project Manager, at (301) 796-2919.

Sincerely,

{See appended electronic signature page}

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

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/s/

REBECCA A MCKNIGHT
08/29/2012

SHULIN DING
08/30/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 203159

REVIEW EXTENSION – MAJOR AMENDMENT

Bayer Healthcare Pharmaceuticals, Inc.
Attention: Jo-Ann Ruane
Associate Director, Global Regulatory Affairs
P.O. Box 1000
Montville, NJ 07045-1000

Dear Ms. Ruane:

Please refer to your December 9, 2011, New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Skyla (levonorgestrel-releasing intrauterine system) 13.5 mg.

On August 10, 2012, we received your solicited major amendment to this application. The receipt date is within three months of the user fee goal date. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is January 9, 2013.

In addition, we are establishing a new timeline for communicating labeling changes and/or postmarketing requirements/commitments in accordance with "PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES – FISCAL YEARS 2008 THROUGH 2012." If major deficiencies are not identified during our review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by November 30, 2012.

If you have any questions, call Charlene Williamson, Regulatory Project Manager, at (301) 796-1025.

Sincerely,

{See appended electronic signature page}

Audrey Gassman, M.D.
Acting Deputy Director
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

AUDREY L GASSMAN
08/15/2012

Jo-Ann Ruane

From: Williamson, Charlene <Charlene.Williamson@fda.hhs.gov>
Sent: Tuesday, July 24, 2012 2:53 PM
To: Jo-Ann Ruane
Cc: Sharon Brown; Williamson, Charlene
Subject: Skyla - Information Request

Jo-Ann,

The Division has an additional information request for your Skyla application.

Please review and respond to the request by August 10, 2012.

Please acknowledge receipt of this email.

Thanks
Charlene

- All availed data obtained subsequent to the 4-month Safety Update Reporting period ending 1/31/12 regarding the to-be-marketed inserter . This would include any additional data from protocol 13362 as well as new data, if available, from protocols 13363 and 14371 both of which initiated enrollment in Sept. 2011. This information could be provided in the same format as presented in the interim CSR A57046.
- In addition, all available data regarding IUD-related complication rates using the new inserter such as expulsions, perforations, endometritis, pelvic inflammatory disease, pregnancies and ectopic pregnancy should be submitted from all on-going studies. All collected data regarding the to-be-marketed IUD complications should be stratified by parity and all of the data should be compared to rates obtained in the primary study A52238.

Jo-Ann Ruane

From: Williamson, Charlene <Charlene.Williamson@fda.hhs.gov>
Sent: Tuesday, July 24, 2012 4:27 PM
To: Jo-Ann Ruane
Cc: Sharon Brown; Williamson, Charlene
Subject: NDA 203159 Information Request (2)

Jo-Ann,

A second request:

Provide narrative summary data by site for study subjects in Study 13362 who underwent sonograms to verify appropriate intrauterine placement of the LCS. This should include (1) the criteria for "investigator discretion" to do a sonogram and (2) percentage of study subjects at these sites who had a placement sonograms vs. those who did not.

Please respond by August 10, 2012.

Please acknowledge receipt of this email.

Thanks

Charlene

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/s/

ZETA-MAE C WILLIAMSON
01/01/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 203159 **INFORMATION REQUEST**

Bayer HealthCare Pharmaceuticals Inc.
Attention: Michael Koenig, Associate Director, Global Regulatory Affairs
PO Box 1000
Montville, NJ 07045-1000

Dear Mr. Koenig:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the levonorgestrel-releasing intrauterine system.

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

1. The differences in device design between the inserter used during the clinical study of Skyla and the one proposed for commercial distribution have the potential to affect the ability to successfully deliver the IUD. Testing should be conducted which evaluates the ability of the insertion device to deliver the IUD to its target location in its intended shape/configuration. This testing should be conducted in a model which simulates worst case clinical conditions and should include a statistically valid sample size. Please provide a copy of this testing along with the results for review.

2. The information that has been provided to establish a shelf life for the Skyla System did not include an evaluation of the inserter. Please either provide the results of testing which supports the maintenance of device functionality over time or provide a justification for why it is not necessary.

3. Based on the information provided on the raw materials, the flange which is a mucosal tissue-contact component of your device includes a new colorant. Since certain colorants are toxicants (e.g., mutagens, carcinogens) that may need additional biocompatibility/toxicity evaluation and are subject to specific regulations, please provide the following additional information for the pink colorant used in the flange:

    a. Material Safety Data Sheet (MSDS) for each colorant.

    b. Identification of other US marketed medical devices by device name, manufacturer, submission number, where the colorant has been previously used, if known.

    c. Whether the colorant confirmed to 21 CFR73 and 21 CFR178 regulations.

If you have questions, call Rebecca McKnight, Regulatory Project Manager, at (301) 796-1765.

Sincerely,

{See appended electronic signature page}

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

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/s/

MOO JHONG RHEE
06/15/2012
Chief, Branch IV

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 203159

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

Bayer Healthcare Pharmaceuticals Inc.
P.O. Box 1000
Montville, New Jersey 07045-1000

ATTENTION: Jo-Ann Ruane
Associate Director, Global Regulatory Affairs

Dear Ms. Ruane:

Please refer to your New Drug Application (NDA) dated December 9, 2011, received December 9, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Levonorgestrel Releasing Intrauterine System, 13.5 mg.

We also refer to your December 20, 2011, correspondence, received December 20, 2011, requesting review of your proposed proprietary name, Skyla. We have completed our review of Skyla and have concluded that it is acceptable.

Your proposed proprietary name, Skyla, 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 December 20, 2011 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, Charlene Williamson at 301-796-1025.

Sincerely,

{See appended electronic signature page}

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

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/s/

CAROL A HOLQUIST
03/08/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 073505

MEETING MINUTES

Bayer Healthcare Pharmaceuticals, Inc.
Attention: Jo-Ann M. Ruane, Associate Director
Global Regulatory Affairs, Women's Healthcare
P.O. Box 1000
Montville, NJ 07045-1000

Dear Ms. Ruane:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Low Dose Levonorgestrel Contraceptive System.

We also refer to the meeting between representatives of your firm and the FDA on July 28, 2011. The purpose of the meeting was to discuss your planned NDA submission.

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

If you have any questions, please call Charlene Williamson, Regulatory Health Project Manager at (301) 796-1025.

Sincerely,

{See appended electronic signature page}

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
OSI Site Level Clinical Dataset Request – See Attachment

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	B
Meeting Category:	Pre-NDA
Meeting Date and Time:	July 28, 2011, 9:30 – 11:00 AM
Meeting Location:	10903 New Hampshire Avenue, Bldg. 22 Room 1417 Silver Spring, MD 20903
Application Number:	IND 073505
Product Name:	Low Dose Levonorgestrel Contraceptive System
Indication:	Pregnancy Prevention
Sponsor/Applicant Name:	Bayer Healthcare Pharmaceuticals, Inc.
Meeting Chair:	Lisa Soule, M.D., Clinical Team Leader
Meeting Recorder:	Charlene Williamson

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
Donna Christner, Ph.D., Pharmaceutical Assessment Lead, Office of New Drug Quality Assessment, (ONDQA)
Kimberly Hatfield, Ph.D., Toxicologist, DRUP
Li Li, Ph.D., Clinical Pharmacologist, Office of Clinical Pharmacology (OCP)
Roy Blay, Ph.D., Reviewer, Good Clinical Assessment Branch, Office of Scientific Investigations (OSI)
Sandra Suarez, Ph.D., Biopharmaceutical Reviewer, ONDQA
Sonia Castillo, Ph.D., Statistician, Office of Biometrics
Charlene Williamson, Regulatory Health Project Manager, DRUP

SPONSOR ATTENDEES

Bayer OY (Finland)
Manja Ahola, Ph.D., Senior Scientist, Pharmaceutical Development

Bayer Healthcare Pharmaceuticals, Inc. (New Jersey)
Sharon Brown, M.S., Director, Global Regulatory Affairs, Women's Healthcare
Patricia Hegarty, M.S., Expert Statistical Analyst - Submissions and Data Standards, Global Statistical Programming
Kimberly Rosen, M.D., Deputy Director, Global Clinical Development
Jo-Ann Ruane, Associate Director, Global Regulatory Affairs, Women's Healthcare
Edio Zampaglione, M.D., FACOG, Senior Director, Medical Affairs, Women's Healthcare

Bayer Healthcare Pharmaceuticals AG (Germany)
Rainer Lewin, M.Sc., Ph.D., Toxicologist, Nonclinical Drug Safety

Sarah Rybowski, M.D., Director, Global Medical Affairs, Women's Healthcare
Pirjo Sallinen, M.Sc., Global Project Leader, Project Management, Women's Healthcare
Thomas Schmelter, Ph.D., Senior Statistician, Global Biostatistics
Klaus Sommer, Ph.D., Global Regulatory Strategist, Global Regulatory Affairs, Women's Healthcare
Christian Zurth, Ph.D., Senior Pharmacokineticist, Global Drug Discovery, Clinical Pharmacology

BACKGROUND

IND 73505 is investigating a low dose levonorgestrel contraceptive system (LCS) for intrauterine contraception. The purpose of this meeting is to discuss and reach concurrence on the content and format of the NDA submission planned for December 2011.

SPONSOR'S QUESTIONS AND THE DIVISION'S RESPONSES

QUALITY (CHEMISTRY, MANUFACTURING AND CONTROLS)

1. *Bayer intends to provide executed batch records for three process validation batches which are different from the primary stability batches. The manufacturing process used differs from the primary stability batches only in the fact that the final, automated production processes have been introduced for these batches. The final manufacturing process introduces some automated assembly steps that were not available for the start of the stability studies. The changes to the manufacturing process would not be expected to have an impact on the stability of the drug product. Does the Agency agree with this approach?*

Division's Response:

If the changes are only to the assembly process, the approach appears acceptable. However, if the changes are to the manufacturing of the drug-containing portions of the intrauterine device (IUD), more information will need to be provided. Provide a tabular comparison of the manufacturing processes used throughout development in the NDA.

2. *The NDA will include one year of stability data on two primary stability batches and 9 months of stability data on a third primary stability batch, and three years of data on batches of product used in clinical trials. Additional data on the primary stability batches can be provided during the NDA review. Does the Division consider these data to be adequate for the NDA filing? Does the Division agree that this approach can be used to support a shelf-life of at least two years?*

Division's Response:

The amount of data appears acceptable for NDA filing. The data on the product used in the clinical trials can be used as supportive data for expiry determination. However, expiry determination is an NDA review issue and will be made after review of all the submitted data.

3. *Bayer intends to provide the information related to the inserter by way of reference to a Device Master File (MAF) submitted by the inserter manufacturer. Does the Division agree with this approach?*

Division's Response:
Yes.

Nonclinical

4. *Does the Division concur that the nonclinical testing strategy for LCS that was described in the initial submission of IND 73,505 is still acceptable for filing of an NDA for LCS12?*

Division's Response:
Yes.

5. *Does the Division concur that the biocompatibility and genetic toxicology studies of the* (b) (4) *removal thread described in the initial submission of IND 73,505, along with the relevant pharmacology and toxicology information for other components of the LCS that were submitted to Bayer's NDA 21-225 for Mirena (levonorgestrel-releasing intrauterine system), may be incorporated in the LCS12 NDA by cross-reference to those applications, and that written and tabular summaries of those studies do not have to be prepared in eCTD format for this NDA?*

Division's Response:
Yes. A tabular listing of titles of studies from NDA 21-225 that will be cross referenced is recommended.

6. *For this NDA in eCTD format, Bayer plans to prepare an updated Nonclinical Overview (Module 2.4) summarizing the pharmacology and toxicology of LNG, and the biocompatibility, genetic toxicology, and local and systemic tolerance studies of the LCS12, its PDMS and PE components, the silver ring, and the LCS12 inserter. Module 2.6 will consist of a tabular overview (Module 2.6.7 Table 1) of all relevant nonclinical studies of the LCS12 and inserter and their components, as presented in this NDA or by cross-reference to NDA 21-225, IND 73,505, and a planned toxicology Information Amendment to IND 73,505. Furthermore, because no new nonclinical studies of the pharmacology or pharmacokinetics of levonorgestrel, the LCS inserter, or their components were conducted, no written or tabular summaries for pharmacology or pharmacokinetics (Modules 2.6.2, 2.6.3, 2.6.4, 2.6.5) will be prepared for this NDA. Does the Division concur with this submission strategy?*

Division's Response:
Yes. However, it does not appear that final study reports have been submitted for all nonclinical studies that the Sponsor has noted will support the application. These include the 9-month local and systemic tolerance in adult cynomolgus monkey study, and recent studies investigating the biocompatibility of the inserter and the silver ring. Submission of summaries of these studies will not be sufficient. Submit with the NDA application any full study reports for supportive nonclinical studies that have not already been submitted to the IND or that are not available via cross-reference to NDA 21-225.

Additional Discussion at the Meeting:
The Sponsor plans to submit a nonclinical amendment to the IND during the 3rd quarter of 2011 consisting of the remaining nonclinical reports that have not previously been submitted to either IND 73505 or NDA 21225. This amendment would include the final report for the 9-month

local and systemic tolerance study in adult cynomolgus monkeys, reports for recent studies investigating the biocompatibility of the LCS12 inserter and its components, reports for studies of the biocompatibility of the silver ring, and several supportive reports. It is the Sponsor's intent that all nonclinical study reports will have been submitted to the IND or referenced from NDA 21-225, and there will be no nonclinical submissions in the forthcoming NDA. This will be acceptable to the Division.

Clinical Pharmacology

7. *Does the Division concur that the studies/investigations described in the Pre-Meeting Information Package will provide sufficient information on the pharmacodynamic and pharmacokinetic characteristics of LNG after LCS12 insertion?*

Division's Response:
The information proposed appears to be acceptable. The full review will be conducted at the time of submission.

8. *The method previously discussed with the Division for the calculation of the in vivo release rates of LNG from LCS12 was based on the assumption of an exponential decline of the residual content of LNG in IUSs obtained from women who prematurely discontinued the study treatment. A new method is proposed, which is based on the in vitro release rates of LNG from LCS12 and which predicts the residual content data by the application of an in vitro/in vivo correlation (IVIVC) model. Does the Division concur that the new approach for calculation of LNG in vivo release rates is an adequate method to describe the in vivo performance of LCS12?*

Division's Response:
The proposal seems reasonable providing the IVIVC model is deemed acceptable by the Division. The Division assumes that the same procedure will be applied for computing the *in vivo* release rate of LNG from LCS16.

9. *During the discussion at the 24 Nov 2009 End-of-Phase 2 meeting, Bayer was encouraged to explore further metrics to assess predictability of the developed IVIVC model. The previous proposal on predictability assessment was based on the calculation of an AUC parameter for the accumulated amount released curve. For the new approach, the AUC of the residual content curve and, additionally, the intercept of this curve will be calculated. Does the Division concur that these two parameters are sufficient to assess the predictability of the IVIVC model?*

Division's Response:
The Division recommends that both approaches, the previous proposal (based on the calculation of an AUC parameter for the accumulated amount released curve) and the new approach (the AUC of the residual content curve and additionally the intercept of this curve) be considered for assessing the internal and external predictability of the proposed IVIVC model. These data are needed because the Division has limited experience in determining the most appropriate procedure to evaluate model predictability for an IVIVC model constructed based on "*ex vivo*" residual content and long-term *in vitro* data.

Clinical

10. Bayer proposes to provide the narrative portions of the Integrated Summary of Efficacy and the Integrated Summary of Safety by cross-reference to the corresponding Module 2 summaries (2.7.3 and 2.7.4, respectively) and to include the tables, appendices, and datasets in Module 5.3.5.3, following Example 4 of the April 2009 Guidance for Industry entitled "Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document." Does the Division concur with Bayer's proposed approach?

Division's Response:

Yes.

11. The proposed NDA will be based on efficacy and safety data from the pivotal Phase 3 study A52238 (protocol 310442) and the Phase 2 study A46796 (protocol 308901). Does the Division concur that the case report forms (CRFs) and narratives provided in the submission include only those for serious adverse events (SAEs), discontinuation due to AEs, pregnancies, and deaths reported from these two studies?

Division's Response:
Yes.

12. LCS12 is a method of contraception with local mechanisms of action. In clinical studies, LCS12 has not shown any evidence of ovulation inhibition. Therefore, Bayer proposes to exclude pregnancies with dates of conception after LCS12 removal in the Pearl Index calculation. Does the Division agree with this approach?

Division's Response:
Pregnancies dated within 7 days after removal of the LCS12 should be counted as "on-treatment" pregnancies, to account for the margin of error in ultrasound dating.

Additional Discussion at the Meeting:
The Sponsor agreed to submit pregnancies dated within the window requested by the Division; the Division will review all post-removal pregnancies on a case-by-case basis. The Sponsor clarified that any pregnancies dated within three months after LCS removal were not documented on case report forms (CRFs), but were recorded on pregnancy forms and pregnancy outcome forms. The Sponsor agreed to provide narratives for the pregnancies in the seven day window after removal.

13. Bayer has provided the proposed Statistical Analysis Plans for the Phase 3 study A52238 (protocol 310442) and the Integrated Analyses (studies A52238 and A46796/protocols 310442 and 308901) for efficacy and safety in this Pre-Meeting Information Package. Does the Division agree with the presented analysis strategy as described in these Statistical Analysis Plans?

Division's Response:
a. Evaluation of efficacy will be based on the 12 month and cumulative 3-year unadjusted Pearl Indices for women 18 to 35 years of age from the phase 3 study A52238 (protocol 310442). Provide unadjusted Pearl Indices for each year of use (e.g., 12 month, 24 month and 36 month) as well.

Additional Discussion at the Meeting:
The Applicant clarified that subjects under 18 were not enrolled, but that an adolescent study is planned to start in Q3 2011 to address European requirements.

b. Both submitted statistical analysis plans should include the following information statement:

- The primary efficacy population consists of those women 18 to 35 years of age from the FAS population.

  Additional Discussion at the Meeting:
  The Division agreed that the bleeding data should be based on women of all ages.

- The total number of on-treatment pregnancies should include pregnancies that occur within 7 days after removal of LCS (see response to Question 12).

  Additional Discussion at the Meeting:
  The Sponsor proposed including this analysis only in the integrated analysis, which will include individual analyses of each study. The relevant data, therefore, would be located in the Integrated Summary of Efficacy and not in the individual Complete Study Report sections of the NDA.

- Total exposure for a subject should be expressed as the number of 28-day cycles, starting from insertion of LCS.
- The 28-day cycle(s) where a concomitant contraceptive method was used should not be included in the total number of 28-day cycles for a subject.

  Additional Discussion at the Meeting:
  The Sponsor will exclude periods with concomitant contraceptive methods used, but noted that this data was captured monthly, not in 28-day cycles. The Sponsor planned to calculate the Pearl Indices based on women-years, and did not intend to do a cycle-based analysis. For women who used backup contraception, the month(s) in which backup was used would be subtracted, allowing partial women-years to be included in the evaluable total.

  Post-Meeting Comment:
  Following further internal discussion, the Division requests that the Sponsor submit the data expressed in 28-day cycle equivalents, as well as in the manner originally proposed. Given that a month in which back-up contraception was used might span two or more 28-day cycles, the Division recommends that the Sponsor develop an algorithm to assign back-up to a single specific 28-day cycle equivalent in such cases. In addition to providing a Pearl Index based on women-years of exposure, the Sponsor should calculate the Pearl Index based on 28-day cycle equivalents. While the Division acknowledges that the LCS is not a cycle-based method, this analysis will allow for consistency with other hormonal contraceptives in calculating the Pearl Index.

  In addition, the bleeding data should be provided based on 28-day cycle equivalents, in the manner recommended by Mischell et al (*Contraception 2007, 75: 11-15).*

- The Pearl Index should be calculated based on women 18 to 35 years of age from the FAS population, the total number of completed 28-day cycles after removing those cycles where another contraceptive method was used, and including all on-treatment

pregnancies. The unadjusted 12 month and unadjusted cumulative 3-year Pearl Index will be the basis for demonstrating efficacy.

- Pearl Indices for women ≥ 36 years of age and for all ages should also be calculated.

Additional Discussion at the Meeting:
The Sponsor noted that only the phase 2 study enrolled women ≥ 36 years, and only 80 women were in this age group. The Division agreed that it would be sufficient to provide analyses for women aged 18-35 and for the whole population, and to omit a specific Pearl Index for the small group of women aged ≥ 36 years.

c. The statistical analysis plan for Study A52238 should include the following information:

- A section for sample size calculation that includes all assumptions and estimates used.
- Adding BMI as a subgroup for analysis in Section 6.2.1 on page 19 of 28.

d. The submission should include a copy of the case report form that was used to collect information about concomitant contraceptive use.

Additional Discussion at the Meeting:
The Sponsor noted that women were asked once monthly if they had used backup contraception during that month (yes/no), so no details about type of contraception used will be available. However, only barrier methods of contraception were allowed per the protocol. Hormonal contraception, if used, should be captured in the concomitant medications dataset.

Because the data were collected once monthly, the Sponsor will be able to determine in which months backup contraception was used, but would not be able to pinpoint it if 28-day cycles are used for data analysis. The Sponsor estimated that only about 4% of women used backup contraception.

e. The following datasets and variables should be included in the submission for Study A52238 (Protocol 310442):

1) Provide a pregnancy information dataset for analysis that includes the following variables:

- Subject Number
- Age (years)
- Treatment
- FAS flag (0 = No, 1 = Yes)
- Date of LCS insertion
- Date of LCS removal
- Date of LCS expulsion
- Flag for partial or total expulsion
- Date of conception
- Flag if conception date was estimated
- Cycle and Day within cycle that pregnancy occurred, for example, coded as C7:D15 for cycle 7, day 15. If the pregnancy occurred outside of the treatment period, then code as, for example, -7 for seven days before LCS insertion or +9 for nine days after LCS removal/expulsion

2) Provide a cycle information dataset for analysis that includes the following variables:

- Subject Number
- Age (years)
- Treatment
- FAS flag (0 = No, 1 = Yes)
- Total number of **completed** 28-day cycles the subject had (if the subject had an on-treatment pregnancy, then include that cycle as a complete cycle and the last cycle in the dataset)
- Cycle Number (if the total number of completed cycles is 27, then there are 27 lines of data for the subject with values 1, 2, 3, 4, 5, 6, 7, …, 26, 27)
- Flag for use of any other birth control method used anytime within a cycle, including condoms (0 = No, 1 = Yes)
- Flag for use of any other birth control method used anytime within a cycle, excluding condoms (0 = No, 1 = Yes)
- Flag for use of condom only anytime within a cycle (0 = No, 1 = Yes)

14. *Bayer's proposal for submitting datasets for studies A52238 (protocol 310442) and A46796 (protocol 308901) and the integrated analyses is described in this Pre-Meeting Information Package. Does the Division agree with the proposal regarding the scope, format, and documentation of the electronic datasets to be submitted?*

Division's Response:
Yes, the Division agrees with the proposal regarding the scope, format, and documentation of the electronic datasets to be submitted.

In addition, submit the line listing datasets, analysis datasets, and program files for the two Studies A52238 (Protocol 310442) and A46796 (Protocol 308901) according to the "Study Data Specifications (v1.6)" document found at:

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm

Specifically, see the **SPECIFICATIONS FOR ORGANIZING DATASETS** section on pages 9 and 10 of the document for how and where the SAS data and SAS program files should be located and organized.

Additional Discussion at the Meeting:
The Sponsor plans to submit in SDTM format with data organized by subject and visit within the domain. The Division agreed that the submitted program files could be limited to those for the primary efficacy analyses. The program files used to generate the primary efficacy analysis datasets should also be submitted.

15. *Bayer proposes to provide post-study Pregnancy Forms that are not part of the Phase 3 Clinical Study Report A52238 (Protocol 310442) as a separate subfolder under the specific study report folder in Module 5.3.5.2. Does the Division concur with this approach?*

Division's Response:
Yes.

16. *Bayer proposes to incorporate reports of scientific literature and post-marketing information in the LCS12 NDA, as required by CFR 314.50(d)(5)(iv), by cross reference the most recent Periodic Safety Update Report (PSUR) and Annual Report submitted to Bayer's approved*

NDA 21-225 for Mirena, a levonorgestrel-releasing intrauterine system that has an initial release rate of approximately 20 µg/day and a 5 year period of use. Does the Division concur with this approach?

Division's Response:
Cross-referencing is acceptable; however, the Sponsor should also provide a narrative summary of the information in the current NDA submission.

Additional Discussion at the Meeting:
The Sponsor will provide the Executive Summary from the most recent Periodic Safety Update Report and the Summary of Safety from the most recent Annual Report (report date in December); this is acceptable to the Division.

17. *Does the Division concur that, based on the summary information provided in this Pre-Meeting Information Package, the proposed content and organization of the clinical information are adequate?*

Division's Response:
Yes.

RISK MANAGEMENT

18. *Does the Division concur that the proposed Risk Management Plan (RMP) as outlined in the Pre-Meeting Information Package is appropriate?*

Division's Response:
Yes.

REGULATORY

19. *Does the Division concur that the clinical studies relevant to the financial disclosure requirements for this submission are the two studies A52238 (protocol 310442) and A46796 (protocol 308901), which are the basis for the Integrated Summary of Efficacy?*

Division's Response:
Yes.

20. *Bayer plans to request a waiver from the Pediatric Research Equity Act (PREA) requirements for pre-menarchal patients because LCS12 will not be indicated for use in those patients. We plan to request that the PREA requirements for post-menarchal pediatric patients be deemed fulfilled by extrapolation of adult data. Does the Division concur with this approach?*

Division's Response:
This approach appears reasonable; however, the Pediatric Research Committee will ultimately make the decision as to whether waiver and extrapolation is appropriate.

21. *Bayer wishes to* [redacted] (b) (4) *Does the Division agree that the strength of the product*

(b) (4)

Division's Response:
It is not acceptable (b) (4)

22. *The LCS12 development program has included a large number of nulliparous women (159 subjects in A46796 and 1,125 subjects in A52238), and Bayer will seek approval of LCS12 for women without respect to parity. Does the Division concur that approval of LCS12 will represent a significant improvement compared with marketed products in that the safety and effectiveness of an LNG-IUS will have been demonstrated for a new subpopulation, i.e., nulliparous women, and that, consequently, the LCS12 NDA is likely to qualify for Priority Review?*

Division's Response:
No.

Additional Discussion at the Meeting:
The Sponsor asked for clarification; the Division noted that Mirena is not specifically contraindicated in nulliparous women, although the labeling recommends use in parous women. In addition, use of IUDs in nulliparous women is strongly encouraged in practice guidelines such as those published by ACOG and in the CDC's Medical Eligibility Criteria for contraceptive use. In clinical practice, Mirena is widely used in nulliparous women.

23. *Based on the summary information provided in this Pre-Meeting Information Package, does the FDA agree that the proposed content and organization of the planned NDA are acceptable and that no barriers to fileability have been identified?*

Division's Response:
In general, the proposed content and organization appear acceptable. See the specific comments below regarding additional information that should be submitted in the NDA.

PRESCRIBING INFORMATION

Proposed prescribing information (PI) submitted with the application must conform to the content and format regulations found at 21 CFR 201.56 and 201.57.

Summary of the Final Rule on the Requirements for Prescribing Information for Drug and Biological Products, labeling guidances, sample tool illustrating Highlights and Table of Contents, an educational module concerning prescription drug labeling, and fictitious prototypes of prescribing information are available at: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm. The Sponsor is encouraged to review the information at this website and use it to draft prescribing information for the application.

OFFICE OF SCIENTIFIC INVESTIGATION (OSI) INFORMATION

Please see attached documents regarding data submission requirements to allow use of the FDA site inspection tool.

Additional Discussion at the Meeting:
OSI noted that the recommendations on data submission continue to evolve; a revised document is attached to the meeting minutes. The Sponsor will provide the requested information for the phase 3 study only, and will place it in Module 5, under the phase 3 study folder. The Sponsor asked if this information could be submitted within two months after NDA submission. OSI noted that the point of using the site inspection selection tool is to allow faster assignment of inspection teams. Particularly where there are foreign inspections (as likely for this NDA), timely completion of inspections during the review clock is challenging. OSI offered to work with the Sponsor to identify which elements are more or less critical to use of the tool, so that the Sponsor might be able to triage and provide the most important information in the NDA submission. OSI requested that all 138 sites be included in the listing, not merely the high enrollers.

MANUFACTURING FACILITIES

To facilitate the inspectional process, the Division of Manufacturing and Product Quality in CDER's Office of Compliance requests that the Sponsor clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with the application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, “Product name, NDA/BLA 012345, Establishment Information for Form 356h.”

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

In addition to the information on the manufacturing sites provided as an attachment to the 356h, full information on these sites should still be provided in the appropriate sections of Modules 2 and 3.

Action Item/Description	Owner	Due Date
The meeting minutes are due to the Sponsor	FDA	August 27, 2011

IND 73505, Bayer LCS
DSI Pre-NDA Request

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct the inspections (Item I and II).

The dataset that is requested as per Item III below, is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of site level datasets will facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 2, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

I. Request for general study related information and specific Clinical Investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

1. Please include the following information in a tabular format in the original NDA for each of the completed Phase 3 clinical trials:
   a. Site number
   b. Principal investigator
   c. Site Location: Address (e.g. Street, City, State, Country) and contact information (i.e., phone, fax, email)
   d. Current Location of Principal Investigator (if no longer at Site): Address (e.g. Street, City, State, Country) and contact information (i.e., phone, fax, email)

2. Please include the following information in a tabular format by site in the original NDA for each of the completed Phase 3 clinical trials:
   a. Number of subjects screened for each site by site
   b. Number of subjects randomized for each site by site
   c. Number of subjects treated who prematurely discontinued for each site by site

3. Please include the following information in a tabular format in the NDA for each of the completed Phase 3 clinical trials:
   a. Location of Trial Master File [actual physical site(s) where documents are maintained and would be available for inspection]
   b. Name, address and contact information of all CROs used in the conduct of the clinical trials
   c. The location (actual physical site where documents are maintained and would be available for inspection) for all source data generated by the CROs with respect to their roles and responsibilities in conduct of respective studies
   d. The location (actual physical site where documents are maintained and would be available for inspection) of sponsor/monitor files (e.g. monitoring master files, drug accountability files, SAE files, etc.)

4. For each pivotal trial provide a sample annotated Case Report Form (if items are provided elsewhere in submission, please describe location or provide a link to requested information).

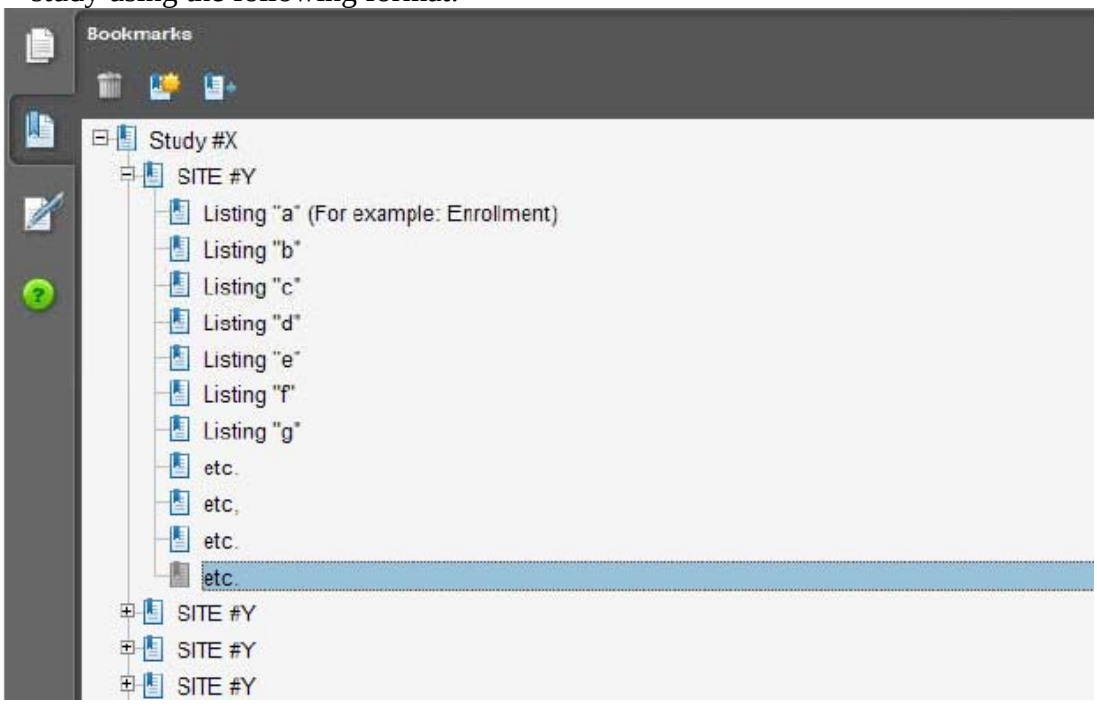
5. For each pivotal trial provide original protocol and all amendments (if items are provided elsewhere in submission, please describe location or provide a link to requested information).

II. Request for Subject Level Data Listings by Site

Please provide, as appropriate:

1. For each pivotal trial: Site-specific individual subject data ("line") listings. For each site provide line listings for:
   a. Listing for each subject/number screened and reason for subjects who did not meet eligibility requirements
   b. Subject listing for treatment assignment (randomization)
   c. Subject listing of drop-outs and subjects that discontinued with date and reason
   d. Evaluable subjects/ non-evaluable subjects and reason not evaluable
   e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
   f. By subject listing, of AEs, SAEs, deaths and dates
   g. By subject listing of protocol violations and/or deviations reported in the NDA, description of the deviation/violation
   h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
   i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
   j. By subject listing, of laboratory tests performed for safety monitoring

2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Electronic submission of site level datasets will facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. Please refer to Attachment 1, "Summary Level Clinical Site Data for Data Integrity Review and Inspection Planning in NDA and BLA Submissions" for further information. We request that you provide a dataset, as outlined, which includes requested data for each pivotal study submitted in your application.

Attachment 1

1 Summary Level Clinical Site Data for Data Integrity Review and Inspection Planning in NDA and BLA Submissions

1.1 Introduction

The purpose of this pilot for electronic submission of a single new clinical site dataset is to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process in support of the evaluation of data integrity.

1.2 Description of the Summary level clinical site dataset

The summary level clinical site data are intended (1) to clearly identify individual clinical investigator sites within an application or supplement, (2) to specifically reference the studies to which those clinical sites are associated, and (3) to present the characteristics and outcomes of the study at the site level.

For each study used to support efficacy, data should be submitted by clinical site and treatment arm for the population used in the primary analysis to support efficacy. As a result, a single clinical site may contain multiple records depending on the number of studies and treatment arms supported by that clinical site.

The site-level efficacy results will be used to support site selection to facilitate the evaluation of the application. To this end, for each study used to support efficacy, the summary level clinical site dataset submission should include site-specific efficacy results by treatment arm and the submission of site-specific effect sizes.

The following paragraphs provide additional details on the format and structure of the efficacy related data elements.

Site-Specific Efficacy Results

For each study and investigator site, the variables associated with efficacy and their variable names are:

- Treatment Efficacy Result (TRTEFFR) – the efficacy result for each primary endpoint, by treatment arm (see below for a description of endpoint types and a discussion on how to report this result)
- Treatment Efficacy Result Standard Deviation (TRTEFFS) – the standard deviation of the efficacy result (treatEffR) for each primary endpoint, by treatment arm
- Site-specific Efficacy Effect Size (SITEEFFE) – the effect size should be the same representation as reported for the primary efficacy analysis
- Site-specific Efficacy Effect Size Standard Deviation (SITEEFFS) – the standard deviation of the site-specific efficacy effect size (SITEEFFE)

- Endpoint (endpoint) – a plain text label that describes the primary endpoint as described in the Define file data dictionary included with each application.

- Treatment Arm (ARM) – a plain text label for the treatment arm that is used in the Clinical Study Report.

In addition, for studies whose primary endpoint is a time-to-event endpoint, include the following data element:

- Censored Observations (CENSOR) –the number of censored observations for the given site and treatment.

If a study does not contain a time-to-event endpoint, record this data element as a missing value.

To accommodate the variety of endpoint types that can be used in analyses please reference the below endpoint type definitions when tabulating the site-specific efficacy result variable by treatment arm, "TRTEFFR."

- Discrete Endpoints – endpoints consisting of efficacy observations that can take on a discrete number of values (e.g., binary, categorical). Summarize discrete endpoints by an event frequency (i.e., number of events), proportion of events, or similar method at the site for the given treatment.

- Continuous Endpoints – endpoints consisting of efficacy observations that can take on an infinite number of values. Summarize continuous endpoints by the mean of the observations at the site for the given treatment.

- Time-to-Event Endpoints – endpoints where the time to occurrence of an event is the primary efficacy measurement. Summarize time-to-event endpoints by two data elements: the number of events that occurred (TRTEFFR) and the number of censored observations (CENSOR).

- Other – if the primary efficacy endpoint cannot be summarized in terms of the previous guidelines, a single or multiple values with precisely defined variable interpretations should be submitted as part of the dataset.

In all cases, the endpoint description provided in the "endpoint" plain text label should be expressed clearly to interpret the value provided in the (TRTEFFR) variable.

The site efficacy effect size (SITEEFFE) should be summarized in terms of the primary efficacy analysis (e.g., difference of means, odds ratio) and should be defined identically for all records in the dataset regardless of treatment.

The Define file for the dataset is presented in Exhibit 1: *Table 1 Clinical Site Data Elements Summary Listing (DE)*. A sample data submission for the variables identified in Exhibit 1 is provided in Exhibit 2. The summary level clinical site data can be submitted in SAS transport file format (*.xpt).

Exhibit 1: Table 1 Clinical Site Data Elements Summary Listing (DE)

Variable Index	Variable Name	Variable Label	Type	Controlled Terms or Format	Notes or Description	Sample Value
1	STUDY	Study Number	Char	String	Study or trial identification number.	ABC-123
2	STUDYTL	Study Title	Char	String	Title of the study as listed in the clinical study report (limit 200 characters)	Double blind, randomized placebo controlled clinical study on the influence of drug X on indication Y
3	DOMAIN	Domain Abbreviation	Char	String	Two-character identification for the domain most relevant to the observation. The Domain abbreviation is also used as a prefix for the variables to ensure uniqueness when datasets are merged.	DE
4	SPONNO	Sponsor Number	Num	Integer	Total number of sponsors throughout the study. If there was a change in the sponsor while the study was ongoing, enter an integer indicating the total number of sponsors. If there was no change in the sponsor while the study was ongoing, enter “1”.	1
5	SPONNAME	Sponsor Name	Char	String	Full name of the sponsor organization conducting the study at the time of study completion, as defined in 21 CFR 312.3(a).	DrugCo, Inc.
6	IND	IND Number	Num	6 digit identifier	Investigational New Drug (IND) application number. If study not performed under IND, enter -1.	010010
7	UNDERIND	Under IND	Char	String	Value should equal "Y" if study at the site was conducted under an IND and "N" if study was not conducted under an IND (i.e., 21 CFR 312.120 studies).	Y
8	NDA	NDA Number	Num	6 digit identifier	FDA new drug application (NDA) number, if available/applicable. If not applicable, enter -1.	021212
9	BLA	BLA Number	Num	6 digit identifier	FDA identification number for biologics license application, if available/applicable. If not applicable, enter -1.	123456
10	SUPPNUM	Supplement Number	Num	Integer	Serial number for supplemental application, if applicable. If not applicable, enter -1.	4
11	SITEID	Site ID	Char	String	Investigator site identification number assigned by the sponsor.	50
12	ARM	Treatment Arm	Char	String	Plain text label for the treatment arm as referenced in the clinical study report (limit 200 characters).	Active (e.g., 25mg), Comparator drug product name (e.g., Drug x), or Placebo
13	ENROLL	Number of Subjects Enrolled	Num	Integer	Total number of subjects enrolled at a given site by treatment arm.	20
14	SCREEN	Number of Subjects Screened	Num	Integer	Total number of subjects screened at a given site.	100

Variable Index	Variable Name	Variable Label	Type	Controlled Terms or Format	Notes or Description	Sample Value
15	DISCONT	Number of Subject Discontinuations	Num	Integer	Number of subjects discontinuing from the study after being enrolled at a site by treatment arm as defined in the clinical study report.	5
16	ENDPOINT	Endpoint	Char	String	Plain text label used to descr be the primary endpoint as described in the Define file included with each application (limit 200 characters).	Average increase in blood pressure
17	ENDPTYPE	Endpoint Type	Char	String	Variable type of the primary endpoint (i.e., continuous, discrete, time to event, or other).	Continuous
18	TRTEFFR	Treatment Efficacy Result	Num	Floating Point	Efficacy result for each primary endpoint by treatment arm at a given site.	0, 0.25, 1, 100
19	TRTEFFS	Treatment Efficacy Result Standard Deviation	Num	Floating Point	Standard deviation of the efficacy result (TRTEFFR) for each primary endpoint by treatment arm at a given site.	0.065
20	SITEEFFE	Site-Specific Efficacy Effect Size	Num	Floating Point	Site effect size with the same representation as reported for the primary efficacy analysis.	0, 0.25, 1, 100
21	SITEEFFS	Site-Specific Efficacy Effect Size Standard Deviation	Num	Floating Point	Standard deviation of the site-specific efficacy effect size (SITEEFFE).	0.065
22	CENSOR	Censored Observations	Num	Integer	Number of censored observations at a given site by treatment arm. If not applicable, enter -1.	5
23	NSAE	Number of Non-Serious Adverse Events	Num	Integer	Total number of non-serious adverse events at a given site by treatment arm. This value should include multiple events per subject and all event types (i.e., not limited to only those that are deemed related to study drug or treatment emergent events).	10
24	SAE	Number of Serious Adverse Events	Num	Integer	Total number of serious adverse events excluding deaths at a given site by treatment arm. This value should include multiple events per subject.	5
25	DEATH	Number of Deaths	Num	Integer	Total number of deaths at a given site by treatment arm.	1
26	PROTVIOL	Number of Protocol Violations	Num	Integer	Number of protocol violations at a given site by treatment arm as defined in the clinical study report. This value should include multiple violations per subject and all violation type (i.e., not limited to only significant deviations).	20
27	FINLMAX	Maximum Financial Disclosure Amount	Num	Floating Point	Maximum financial disclosure amount ($USD) by any single investigator by site. Under the applicable regulations (21 CFR Parts 54, 312, 314, 320, 330, 601, 807, 812, 814, and 860). If unable to obtain the information required to the corresponding statements, enter -1.	20000.00
28	FINLDISC	Financial Disclosure Amount	Num	Floating Point	Total financial disclosure amount ($USD) by site calculated as the sum of disclosures for the principal investigator and all sub-investigators to include all required parities. Under the applicable regulations (21 CFR Parts 54, 312, 314, 320, 330, 601, 807, 812, 814, and 860). If unable to obtain the information required to the corresponding statements, enter -1.	25000.00

Variable Index	Variable Name	Variable Label	Type	Controlled Terms or Format	Notes or Description	Sample Value
29	LASTNAME	Investigator Last Name	Char	String	Last name of the investigator as it appears on the FDA 1572.	Doe
30	FRSTNAME	Investigator First Name	Char	String	First name of the investigator as it appears on the FDA 1572.	John
31	MINITIAL	Investigator Middle Initial	Char	String	Middle initial of the investigator, if any, as it appears on the FDA 1572.	M
32	PHONE	Investigator Phone Number	Char	String	Phone number of the primary investigator. Include country code for non-US numbers.	44-555-555-5555
33	FAX	Investigator Fax Number	Char	String	Fax number of the primary investigator. Include country code for non-US numbers.	44-555-555-5555
34	EMAIL	Investigator Email Address	Char	String	Email address of the primary investigator.	john.doe@mail.com
35	COUNTRY	Country	Char	ISO 3166-1-alpha-2	2 letter ISO 3166 country code in which the site is located.	US
36	STATE	State	Char	String	Unabbreviated state or province in which the site is located. If not applicable, enter NA.	Maryland
37	CITY	City	Char	String	Unabbreviated city, county, or village in which the site is located.	Silver Spring
38	POSTAL	Postal Code	Char	String	Postal code in which site is located. If not applicable, enter NA.	20850
39	STREET	Street Address	Char	String	Street address and office number at which the site is located.	1 Main St, Suite 100

The following is a fictional example of a data set for a placebo-controlled trial. Four international sites enrolled a total of 205 subjects who were randomized in a 1:1 ratio to active or placebo. The primary endpoint was the percent of responders. The site-specific efficacy effect size (SITEEFFE) is the difference between the active and the placebo treatment efficacy result. Note that since there were two treatment arms, each site contains 2 rows in the following example data set and a total of 8 rows for the entire data set.

Exhibit 2: Example for Clinical Site Data Elements Summary Listing (Table 1)

STUDY	STUDYTL	DOMAIN	SPONNO	SPONNAME	IND	UNDERIND	NDA	BLA	SUPPNUM	SITEID	ARM	ENROLL	SCREEN	DISCONT
ABC-123	Double blind…	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	001	Active	26	61	3
ABC-123	Double blind…	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	001	Placebo	25	61	4
ABC-123	Double blind…	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	002	Active	23	54	2
ABC-123	Double blind…	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	002	Placebo	25	54	4
ABC-123	Double blind…	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	003	Active	27	62	3
ABC-123	Double blind…	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	003	Placebo	26	62	5
ABC-123	Double blind…	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	004	Active	26	60	2
ABC-123	Double blind…	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	004	Placebo	27	60	1

ENDPOINT	ENDTYPE	TRTEFFR	TRTEFFS	SITEEFFE	SITEEFFS	CENSOR	NSAE	SAE	DEATH	PROTVIOL	FINLMAX	FINLDISC	LASTNAME	FRSTNAME
Percent Responders	Binary	0.48	0.0096	0.34	0.0198	-1	0	2	0	1	-1	-1	Doe	John
Percent Responders	Binary	0.14	0.0049	0.34	0.0198	-1	2	2	0	1	-1	-1	Doe	John
Percent Responders	Binary	0.48	0.0108	0.33	0.0204	-1	3	2	1	0	45000.00	45000.00	Washington	George
Percent Responders	Binary	0.14	0.0049	0.33	0.0204	-1	0	2	0	3	20000.00	45000.00	Washington	George
Percent Responders	Binary	0.54	0.0092	0.35	0.0210	-1	2	2	0	1	15000.00	25000.00	Jefferson	Thomas
Percent Responders	Binary	0.19	0.0059	0.35	0.0210	-1	3	6	0	0	22000.00	25000.00	Jefferson	Thomas
Percent Responders	Binary	0.46	0.0095	0.34	0.0161	-1	4	1	0	0	0.00	0.00	Lincoln	Abraham
Percent Responders	Binary	0.12	0.0038	0.34	0.0161	-1	1	2	0	1	0.00	0.00	Lincoln	Abraham

MINITIAL	PHONE	FAX	EMAIL	COUNTRY	STATE	CITY	POSTAL	STREET
M	555-123-4567	555-123-4560	John@mail.com	RU	Moscow	Moscow	103009	Kremlin Road 1
M	555-123-4567	555-123-4560	John@mail.com	RU	Moscow	Moscow	103009	Kremlin Road 1
	020-3456-7891	020-3456-7890	george@mail.com	GB	Westminster	London	SW1A 2	10 Downing St
	020-3456-7891	020-3456-7890	george@mail.com	GB	Westminster	London	SW1A 2	10 Downing St
	01-89-12-34-56	01-89-12-34-51	tom@mail.com	FR	N/A	Paris	75002	1, Rue Road
	01-89-12-34-56	01-89-12-34-51	tom@mail.com	FR	N/A	Paris	75002	1, Rue Road
	555-987-6543	555-987-6540	abe@mail.com	US	Maryland	Rockville	20852	1 Rockville Pk.
	555-987-6543	555-987-6540	abe@mail.com	US	Maryland	Rockville	20852	1 Rockville Pk.

Attachment 2

Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named "BIMO [list study ID, followed by brief description of file being submitted]." In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be "bimo." Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be "clinsite.xpt."

DSI Pre-NDA Request Item[1]	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:

C. It is recommended, but not required, that a Reviewer's Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be "BIMO Reviewer Guide." The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

[1] Please see the OSI Pre-NDA Request document for a full description of requested data files

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1
(http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf)

FDA eCTD web page
(http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm)

For general help with eCTD submissions: ESUB@fda.hhs.gov

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

/s/

LISA M SOULE
08/24/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 073505

MEETING MINUTES

Bayer Healthcare Pharmaceuticals, Inc.
Attention: Jo-Ann Ruane
Associate Director, Global Regulatory Affairs
P.O. Box 1000
Montville, NJ 07045-1000

Dear Ms. Ruane:

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

We also refer to the meeting between representatives of your firm and the FDA on November 24, 2009. The purpose of the meeting was to discuss proposed modifications to your development program based on the recently available results of a three year, phase 2 study (Protocol 308901).

A 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, call Charlene Williamson, Regulatory Project Manager, at (301) 796-1025.

Sincerely,

{See appended electronic signature page}

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

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: End of Phase 2

Meeting Date and Time: November 24, 2009
Meeting Location: 10:30 – 12:00 PM

Application Number: IND 073505
Product Name: Low-Dose levonorgestrel Contraceptive System
Indication: Intrauterine contraception for up to 3 years
Sponsor/Applicant Name: Bayer Healthcare Pharmaceuticals, Inc.

Meeting Chair: Lisa Soule, M.D.
Meeting Recorder: Charlene Williamson

FDA ATTENDEES

Lisa Soule, M.D., Clinical Team Leader, DRUP
Ronald Orleans, M.D., Medical Officer, DRUP
Doanh Tran, Ph.D., Clinical Pharmacology Reviewer, Office of Clinical Pharmacology
Donna Christner, Ph.D., Pharmaceutical Assessment Lead, Office of New Drug Quality Assessment (ONDQA)
Sandra Suarez-Sharp, Ph.D., Senior Biopharmaceutics Reviewer, ONDQA/Biopharmaceutics
Jennifer Mercier, Chief, Project Management Staff, DRUP
Charlene Williamson, Regulatory Project Manager, DRUP

SPONSOR ATTENDEES

Manja Ahola, Ph.D., Senior Scientist, Pharmaceutical Development, BSP Oy
Antonio Costales, MD, Medical Director, US Medical Affairs, Women's Healthcare, BHP
Jo-Ann Ruane, Associate Director, Global Regulatory Affairs, Women's Healthcare, BHP
Pirjo Sallinen, M.Sc., Global Project Leader, Project Management, Women's Healthcare, BSP AG3
Ilka Schellschmidt, MD, Executive Director Female Contraception, Global Clinical Development, Women's Healthcare, BSP AG
Thomas Schmelter, Ph.D., Senior Statistician, Global Biostatistics, BSP AG4
Klaus Sommer, Ph.D. - Global Regulatory Strategist, Global Regulatory Affairs, Women's Healthcare, BSP AG
Christian Zurth, Ph.D., Senior Pharmacokineticist, Global Medical Development, Clinical Pharmacology, BSP AG

BACKGROUND

Low-Dose Levonorgestrel Contraceptive System is an intrauterine contraceptive with a proposed treatment duration of 3 (b) (4) years. The purpose of the meeting was to discuss the recently obtained results of a three-year phase 2 study, and to obtain the Division's concurrence with respect to modifications regarding the clinical development plan, establishment of a Level A *in vivo in vitro* correlation (IVIVC), and bridging the phase 2 and phase 3 formulations.

SPONSOR QUESTIONS AND THE DIVISION'S RESPONSES

Clinical

Question 1:

Bayer proposes to investigate the efficacy and safety of LCS16 for a treatment duration of 5 years by extending the LCS16 arm of Protocol 310442 from 3 to 5 years. Does the Division concur that the extension of the study as proposed and the conservative estimate of 237 women completing the 5 years of treatment as outlined in the pre-meeting package will be sufficient to assess the safety and efficacy of LCS16 for a 5-year period of use?

Division Response:

The Division requests that a minimum of 200 women complete the full duration of treatment for which approval is sought. Review of contraceptive efficacy in years 4 and 5 will be based upon the acceptability of the upper bound of the confidence interval around the Pearl Index.

In addition to the Pearl Index and its 95% confidence interval, the life table estimate and its 95% confidence interval should be included in the efficacy analysis.

The Division also requests that, at a minimum, pregnancy testing be performed at Month 48, as well as at Months 36 and 60 as proposed.

To ensure that the product will perform as anticipated in years 4 and 5, the Division recommends that the Sponsor evaluate in a timely manner (within 90 days) the serum levonorgestrel (LNG) concentrations from the first 15 subjects who complete visits at 36, 42, 48, and 54 months. The observed serum LNG concentrations should be evaluated for any significant deviation from the expected concentration. If the serum concentrations were unexpectedly low (or undetectable), more frequent pregnancy testing should be instituted, and stopping rules based on an unacceptable pregnancy rate should be implemented.

Additional Discussion at the Meeting:

The Sponsor proposed an alternative approach to the Division's recommended serum sampling at Months 36, 42, 48 and 54. The Sponsor stated that serum concentrations are highly variable, and at the end of Year 2, 10% of samples in the LCS12 group are already below the limits of quantitation (LoQ) of 30 pg/ml. For this reason, extrapolating from 15 subjects would be of limited value. Also, serum concentrations are not predictive of efficacy. Instead, the Sponsor proposed evaluating residual content data, with provision for more frequent

pregnancy testing if residual content levels deviated strongly from those observed in the phase 2 study. The Division expressed concern about the discontinuation rate in Years 4 and 5 of the trial; if few women discontinue, there will be few removed devices from which to evaluate residual content. The Sponsor noted that the discontinuation rate per six month period ranges from 6-12% in the current trials, and that women frequently change their minds and discontinue for desired pregnancy. The Sponsor would expect to have about 40 samples to assess per six month period. The Division agreed to the Sponsor's approach of evaluating residual content, provided that samples were assessed at least every three months, regardless of the batch size available. The Sponsor agreed to this stipulation.

The Sponsor described its internal monitoring of pregnancies, which it feels supplants the need for formal stopping rules. Pregnancies are reported within 24 hours and the Sponsor can immediately calculate updated Pearl Indices, based on current exposure. The Sponsor internally has determined that a Pearl Index above 1.0 would not be acceptable to support continued study; in addition to the Pearl Index, the proportion of pregnancies that are ectopic is also a consideration. Currently, the ectopic rate is about 50% of all pregnancies, which the Sponsor reported is similar to that of Mirena.

Additional Clinical Pharmacology Comments:

1. Timely assessment of *in vivo* release rate from discontinued subjects should be considered.
2. The Division recommends that the Sponsor characterize the serum LNG pharmacokinetic (PK) after removal of the intrauterine system (IUS). PK assessments should be done at Day 1, 2, 7, and 14 post-removal. This could be performed as part of the PK subgroup (group S3) or via sparse samplings of a larger population.

   Additional Discussion at the Meeting:
   The Sponsor noted that LNG concentrations decline immediately (within 1 day) after removal, approaching zero by Day 3, according to Mirena data presented in the meeting package (Mirena Study A10982). There was no sign of a depot effect with this higher-dose product. Given an LNG terminal $t_{1/2}$ of about 17 hours and an expected concentration at Year 5 of 71 pg/ml for the LCS16, the serum LNG concentration would be expected to be < LoQ by Day 2 after IUS removal. The Sponsor noted that the LCS formulation is very similar to that of Mirena, although LCS has a "burst" effect (b) (4) The Division agreed, given the similarity of composition to that of Mirena as stated by the Sponsor, that the data from Mirena would be acceptable to characterize whether there is a depot effect of LCS following its removal.

3. Provide the range of body weight and body mass index in subjects enrolled in Study 310442.

Additional Discussion at the Meeting:
The Sponsor had no weight or BMI restrictions, and provided data showing that subjects in US sites were of greater weight/higher BMI than those in the rest of the world, but that there was a good range over all sites (e.g., 38 to 72 kg, BMI of 15 to 58 kg/m^2). The Sponsor plans to evaluate serum concentrations by body weight and BMI in the population PK analysis; data from Mirena suggests some dependence of serum concentration on body weight.

Question 2:

The proposed approach to establishing and validating a Level A IVIVC for LCS is described in the pre-meeting package. Does the Division concur that the developed in vitro/in vivo correlation (IVIVC) is valid and that this approach is sufficient after external validation with the Phase 3 data to establish a Level A IVIVC for LCS?

Division Response:
The approach used to develop the *in vitro/in vivo* correlation (IVIVC) for the Levonorgestrel Contraceptive System **(**LCS) by plotting the cumulative percentages released *in vivo* against the cumulative percentages released from *in vitro* release rate samples at the same time points for both test formulations seems reasonable. However, the following information is needed to reach a conclusion on the acceptability of the model and its validation:

- Dissolution method development and validation
- Rationale and detailed information on the procedure for internal predictability. There is not enough detailed information in the meeting package to reach a conclusion on the acceptability of the proposed method to evaluate predictability. Besides the proposed point-to-point comparison for calculating % PE, also consider a metric that encompasses the overall *in vivo* release elapsed up to the last time point measured (e.g. slope and intercept of the profiles).

Additional Discussion at the Meeting:
The Sponsor proposed that AUC, rather than slope and intercept, be used for calculating prediction error percent (% PE) for the in vivo release. The Sponsor would provide both point-to-point comparisons and AUC comparisons to evaluate internal predictability. The Division agreed to review the data based on AUC, but cannot concur that this is the appropriate metric prior to review. The Division prefers that the criteria for acceptability be based on mean rather than the Sponsor's proposed median values. The Sponsor is encouraged to explore other metrics as well.

Question 3:

Bayer has not implemented the majority of the Phase 2 to Phase 3 formulation changes that were anticipated when the pre-IND pre-meeting package was submitted (March 1,

2006). Only the addition of the silver ring and other minor modifications that are due to manufacturing optimization during Phase 2 and 3 as described in the package were implemented. In light of the established IVIVC (as described in the pre-meeting package), Bayer is proposing an alternate approach to demonstrating the similarity of the Phase 2 and Phase 3 products. Does the Division concur that a bioequivalence approach as reflected in the Division's May 1, 2006 final minutes of the (cancelled) pre-IND meeting and as acknowledged in the IND is no longer needed and that the alternate approach described in the current pre-meeting package is acceptable?

Division Response:

From a clinical perspective, such bridging will not be necessary if the pivotal data to support marketing approval will be provided by the phase 3 program. However, the ability to demonstrate similarity between two products may be important to support changes made post-approval. In those cases, the alternate approach proposed is not acceptable. In the presence of an acceptable IVIVC, the requirements of *in vivo* bioequivalence can be waived based on dissolution profiles. However, rather than calculating the f2 similarity factor of the *in vitro* release profiles as proposed, the Division requests that the predicted mean *in vivo* release rate of the test product (e.g., post-approval change) should be no more than 20% different from that of the reference product (e.g., pre-approval change). In addition, both products should meet the application/compendial dissolution specifications (refer to *Guidance for Industry - Extended Release Oral Dosage Forms: Development, Evaluation and Application of In Vitro/In Vivo Correlation*).

Additional Discussion at the Meeting:

The Division asked whether the Sponsor plans to rely on phase 2 data for safety and efficacy; the Sponsor plans to pool data from phase 2 and 3, as well as providing data from the individual studies. In this case, the Sponsor will need to bridge the formulations used in phase 2 and 3, and this will be problematic if the IVIVC fails. From a clinical perspective, it appears that phase 3 Study 310442 is likely to provide sufficient numbers of subjects and exposure cycles to support safety and efficacy even if the phase 2 data cannot be relied upon.

Additional Biopharmaceutics Comments:

The proposal to test the *in vitro* release only (b) (4) as part of the short-term *in vitro* release rate is not acceptable. To justify a new testing protocol, the amount of drug released in the proposed media should be obtained at time points covering the initial, mid-point, and end of the test period. Individual release rates and the means for each IUS at each time point in the sample analysis should be provided. In addition, provide the developmental report describing the rationale behind the choice of media, testing conditions, and acceptance criteria for both short-term and long-term dissolution method in the NDA submission.

Additional Discussion at the Meeting:

The Sponsor provided data from five LCS12 batches at seven time points; from

these data, the Sponsor has selected (b) (4) as the specification. (b) (4) shows great variability, so the Sponsor proposed to us (b) (4) he Division was concerned, particularly from the perspective of safety, that using (b) (4) as the first time point would miss the early portion of the curve, where the burst effect is apparent.

Post-Meeting Comment:
The Division does not agree with the proposal to use (b) (4) as the early time point. Sufficient sampling time points as early as Day 1 or Day 2 should be taken to characterize accurately the entire short-term *in vitro* release rate profile of LCS.

Action Item/Description	Owner	Due Date
Meeting Minutes	FDA	December 23, 2009

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
IND-73505	GI-1	BAYER HEALTHCARE PHARMACEUTICALS INC	LEVONORGESTREL CONTRACEPTIVE SYSTEM

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

/s/

LISA M SOULE
12/17/2009

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 203159 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type:
Proprietary Name: Skyla Intrauterine Contraceptive System Established/Proper Name: levonorgestrel Dosage Form:		Applicant: Bayer Healthcare Pharmaceuticals, Inc. Agent for Applicant (if applicable):
RPM: Charlene Williamson		Division: Reproductive and Urologic Products

NDAs and NDA Efficacy Supplements:

NDA Application Type: ☒ 505(b)(1) ☐ 505(b)(2)
Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2)

(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.)

505(b)(2) Original NDAs and 505(b)(2) NDA supplements:

Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):

Provide a brief explanation of how this product is different from the listed drug.

☐ This application does not reply upon a listed drug.
☐ This application relies on literature.
☐ This application relies on a final OTC monograph.
☐ This application relies on (explain)

For ALL (b)(2) applications, two months prior to EVERY action, review the information in the 505(b)(2) Assessment and submit the draft[2] to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.

On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.

☐ No changes ☐ Updated Date of check:

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.

❖ Actions	
• Proposed action • User Fee Goal Date is January 9, 2013	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☒ None

[1] The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 5) lists documents to be included in the Action Package.

For resubmissions, (b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., nrew listed drug, patent certification revised).

❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☐ Received
❖ Application Characteristics [3]	

Review priority: ☒ Standard ☐ Priority
Chemical classification (new NDAs only): 3

☐ Fast Track
☐ Rolling Review
☐ Orphan drug designation

☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

☐ Submitted in response to a PMR
☐ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

REMS: ☐ MedGuide
☐ Communication Plan
☐ ETASU
☐ MedGuide w/o REMS
☐ REMS not required

Comments:

❖ BLAs only: Ensure *RMS-BLA Product Information Sheet for TBP* and *RMS-BLA Facility Information Sheet for TBP* have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	☐ Yes, dates
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☒ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes ☐ No
• Press Office notified of action (by OEP)	☒ Yes ☐ No
• Indicate what types (if any) of information dissemination are anticipated	☒ None ☐ HHS Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other

[3] 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	
• Is approval of this application blocked by any type of exclusivity?	☒ No ☐ Yes
• NDAs and BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	☒ No ☐ Yes If, yes, NDA/BLA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application)? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? *(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.)*	☒ No ☐ Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
• 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.	☒ Verified ☐ Not applicable because drug is an old antibiotic.
• 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.	21 CFR 314.50(i)(1)(*i*)(A) ☐ Verified 21 CFR 314.50(i)(1) ☐ (ii) ☐ (iii)
• [505(b)(2) applications] If the application includes a **paragraph III** 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).	☐ No paragraph III certification Date patent will expire
• [505(b)(2) applications] For **each paragraph IV** 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). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (*Summary Reviews*)).*	☐ N/A (no paragraph IV certification) ☐ 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).*

(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? (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). *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*).* *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.*	☐ Yes ☐ No
CONTENTS OF ACTION PACKAGE	
❖ Copy of this Action Package Checklist[4]	yes
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included
Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Action(s) and date(s) January 9, 2013
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	January 9, 2013
• Original applicant-proposed labeling	December 9, 2011
• Example of class labeling, if applicable	

[4] Fill in blanks with dates of reviews, letters, etc.

Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☐ Medication Guide ☒ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☐ None
• Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	January 9, 2013
• Original applicant-proposed labeling	December 9, 2011
• Example of class labeling, if applicable	
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	Yes
❖ Proprietary Name • Acceptability/non-acceptability letter(s) - • Review(s) – *03/08/2012; 07/20/2012; and 10/23/2012* • *Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name.*	AP- 10/23/2012
❖ Labeling reviews *(indicate dates of reviews and meetings)*	☒ RPM 02/10/2012 ☒ DMEPA 12/17/2012;11/15/2012 ☒ DMPP/PLT (DRISK) 12/05/2012 ☒ ODPD (DDMAC) 12/13/2012 ☒ SEALD 01/07/2013 ☐ CSS ☐ Other reviews
Administrative / Regulatory Documents	
❖ Administrative Reviews *(e.g., RPM Filing Review[5]/Memo of Filing Meeting) (indicate date of each review)*	02/21/2012
❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte	☒ Not a (b)(2)
❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment *(indicate date)*	☒ Not a (b)(2)
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☒ Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No
• This application is on the AIP o If yes, Center Director's Exception for Review memo *(indicate date)* o If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☒ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC August 15, 2012 If PeRC review not necessary, explain: _____ • Pediatric Page/Record *(approvals only, must be reviewed by PERC before finalized)*	☒ Included

[5] Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

❖ 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 *(include certification)*	☒ Verified, statement is acceptable
❖ Outgoing communications *(letters, including response to FDRR (do not include previous action letters in this tab), emails, faxes, telecons)*	Various
❖ Internal memoranda, telecons, etc.	None
❖ Minutes of Meetings	
• Regulatory Briefing *(indicate date of mtg)*	☒ No mtg
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☒ N/A or no mtg
• Pre-NDA/BLA meeting *(indicate date of mtg)*	☐ No mtg 07/28/2011
• EOP2 meeting *(indicate date of mtg)*	☐ No mtg 11/24/2009
• Other milestone meetings (e.g., EOP2a, CMC pilots) *(indicate dates of mtgs)*	
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available *(do not include transcript)*	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☒ None
Division Director Summary Review *(indicate date for each review)*	☐ None January 9, 2013
Cross-Discipline Team Leader Review *(indicate date for each review)*	☐ None January 9, 2013
PMR/PMC Development Templates *(indicate total number)*	☒ None
Clinical Information[6]	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	See CDTL Review
• Clinical review(s) *(indicate date for each review)*	12/27/2012
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	See Clinical Review – Page 18
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ Not applicable
❖ Risk Management • REMS Documents and Supporting Statement *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	☒ None

[6] Filing reviews should be filed with the discipline reviews.

OSI Clinical Inspection Review Summary(ies) *(include copies of OSI letters to investigators)*	☐ None requested 08/12/2012;10/23/2012;11/16/2012
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☒ None
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☒ None
Statistical Team Leader Review(s) *(indicate date for each review)*	☒ None 12/04/2012
Statistical Review(s) *(indicate date for each review)*	☐ None 12/04/2012
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ None
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☐ None 12/5/2012
Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None 12/5/2012
❖ DSI Clinical Pharmacology Inspection Review Summary *(include copies of OSI letters)*	☒ None
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☒ None
• Supervisory Review(s) *(indicate date for each review)*	☐ None 11/23/2012
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None 11/21/2012
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None
❖ OSI Nonclinical Inspection Review Summary *(include copies of OSI letters)*	☒ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	☒ None
• Branch Chief/Team Leader Review(s) *(indicate date for each review)*	☒ None
• Product quality review(s) including ONDQA biopharmaceutics reviews *(indicate date for each review)*	☐ None 08/06/2012
❖ Microbiology Reviews ☒ NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) *(indicate date of each review)* ☐ BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) *(indicate date of each review)*	☐ Not needed 03/26/2012
Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date of each review)*	☐ None 07/08/2012;10/18/2012(2); 11/2/2012;11/7/2012(2);12/19/201

	2; 12/21/2012
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	08/06/2012 - Page 60
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Facilities Review/Inspection	
☒ NDAs: Facilities inspections (include EER printout) *(date completed must be within **2 years** of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites[7])*	Date completed: ☒ Acceptable ☐ Withhold recommendation ☐ Not applicable
☐ BLAs: TB-EER *(date of most recent TB-EER must be within **30 days** of action date) (original and supplemental BLAs)*	Date completed: ☐ Acceptable ☐ Withhold recommendation
❖ NDAs: Methods Validation *(check box only, do not include documents)*	☒ Completed ☐ Requested ☐ Not yet requested ☐ Not needed (per review)

[7] 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.