

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

206229Orig1s000

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 206229

SUPPL #

HFD #

Trade Name Liletta intrauterine system

Generic Name levonorgestrel-releasing

Applicant Name Medicines360

Approval Date, If Known February 26, 2015

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)(2)

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?

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

YES NO

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

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

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

YES NO

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

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

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

YES NO

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

NDA# 203159 Skyla IUS
NDA# 21225 Mirena
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:

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"):

- 1) Study M360-L102 - A Phase 3, Multi-Center, Open-Label Study of a Levonorgestrel-Releasing Intrauterine System for Long-Term, Reversible Contraception
- 2) Study M360-L104 - A Phase 1, Multi-Center Study to Assess the Performance of a LNG20 Intrauterine System Inserter

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 # 105836 YES !
! ! NO
! Explain:

Investigation #2
IND # 105836 YES !
! ! NO
! Explain:

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

/s/

ZETA-MAE C WILLIAMSON
02/26/2015

AUDREY L GASSMAN
02/26/2015

PEDIATRIC PAGE
(Complete for all filed original applications and efficacy supplements)

NDA/BLA#: 206229 Supplement Number: _____ NDA Supplement Type (e.g. SE5): _____

Division Name: Bone, Reproductive and Urologic Products PDUFA Goal Date: February 28, 2015 Stamp Date: 4/30/2014

Proprietary Name: TBD

Established/Generic Name: Levonorgestrel

Dosage Form: IUS

Applicant/Sponsor: Medicines360

Indication(s) previously approved (please complete this question for supplements and Type 6 NDAs only):

- (1) _____
(2) _____
(3) _____
(4) _____
-

Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s): 1
(Attach a completed Pediatric Page for each indication in current application.)

Indication: intrauterine contraception for up to 3 years

Q1: Is this application in response to a PREA PMR? Yes Continue
No Please proceed to Question 2.

If Yes, NDA/BLA#: _____ Supplement #: _____ PMR #: _____

Does the division agree that this is a complete response to the PMR?

- Yes. Please proceed to Section D.
 No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

Q2: Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

(a) NEW active ingredient(s) (includes new combination); indication(s); dosage form; dosing regimen; or route of administration?*

(b) No. PREA does not apply. **Skip to signature block.**

* **Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.**

Q3: Does this indication have orphan designation?

- Yes. PREA does not apply. **Skip to signature block.**
 No. Please proceed to the next question.

Q4: Is there a full waiver for all pediatric age groups for this indication (check one)?

- Yes: (Complete Section A.)
 No: Please check all that apply:
 Partial Waiver for selected pediatric subpopulations (Complete Sections B)
 Deferred for some or all pediatric subpopulations (Complete Sections C)
 Completed for some or all pediatric subpopulations (Complete Sections D)
 Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
 Extrapolation in One or More Pediatric Age Groups (Complete Section F)

(Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**)

- Necessary studies would be impossible or highly impracticable because:
 - Disease/condition does not exist in children (**0-12 years old**)
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed): _____
- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

			Reason (see below for further detail):				
	minimum	maximum	Not feasible [#]	Not meaningful therapeutic benefit [*]	Ineffective or unsafe [†]	Formulation failed ^Δ	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

Not feasible:

- Necessary studies would be impossible or highly impracticable because:
 - Disease/condition does not exist in children
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed): _____

***** Not meaningful therapeutic benefit:

- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL (cderpmhs@fda.hhs.gov) OR AT 301-796-0700.

pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

Δ Formulation failed:

- Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.*)

Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for selected pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				Reason for Deferral			Applicant Certification †
Population	minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received	
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Date studies are due (mm/dd/yy): _____							

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL (cderpmhs@fda.hhs.gov) OR AT 301-796-0700.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):					
Population		minimum	maximum	PeRC Pediatric Assessment form attached?.	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input checked="" type="checkbox"/>	Other	<u>12</u> yr. <u>0</u> mo.	<u>16</u> yr. <u>11</u> mo.	Yes <input type="checkbox"/>	No <input checked="" type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:

Population		minimum	maximum
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL (cderpmhs@fda.hhs.gov) OR AT 301-796-0700.

If there are additional indications, please complete the attachment for each one of those indications. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

(Revised: 6/2008)

NOTE: If you have no other indications for this application, you may delete the attachments from this document.

Attachment A

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

Indication #2: _____**Q1:** Does this indication have orphan designation?

- Yes. PREA does not apply. **Skip to signature block.**
- No. Please proceed to the next question.

Q2: Is there a full waiver for all pediatric age groups for this indication (check one)?

- Yes: (Complete Section A.)
- No: Please check all that apply:
- Partial Waiver for selected pediatric subpopulations (Complete Sections B)
 - Deferred for some or all pediatric subpopulations (Complete Sections C)
 - Completed for some or all pediatric subpopulations (Complete Sections D)
 - Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
 - Extrapolation in One or More Pediatric Age Groups (Complete Section F)
- (Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**)

- Necessary studies would be impossible or highly impracticable because:
- Disease/condition does not exist in children
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed): _____
- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

		Reason (see below for further detail):					
		minimum	maximum	Not feasible [#]	Not meaningful therapeutic benefit [*]	Ineffective or unsafe [†]	Formulation failed ^Δ
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

Not feasible:

Necessary studies would be impossible or highly impracticable because:

Disease/condition does not exist in children

Too few children with disease/condition to study

Other (e.g., patients geographically dispersed): _____

***** Not meaningful therapeutic benefit:

Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

Δ Formulation failed:

Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.*)

Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Section C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so,

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL (cderpmhs@fda.hhs.gov) OR AT 301-796-0700.

proceed to Section F).. Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for some or all pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				Reason for Deferral			Applicant Certification †
Population	minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received	
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Date studies are due (mm/dd/yy): _____							

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):

Population		minimum	maximum	PeRC Pediatric Assessment form attached?	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:

Population		minimum	maximum
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population	minimum	maximum	Extrapolated from:	
			Adult Studies?	Other Pediatric Studies?
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

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

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 6/2008)

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

/s/

ZETA-MAE C WILLIAMSON
11/17/2014

Note: The PeRC review of this product will likely occur *after* the Review Division checks this completed document into DARRTS. The PeRC's recommendation, which may differ from the information in this document, will be described in the PeRC meeting minutes. PeRC meeting minutes are linked in DARRTS to the INDs and applications discussed during each meeting.

Dear Review Division:

The attached template includes the necessary documentation to facilitate the *required* Pediatric Review Committee (PeRC) review of Waivers, Deferrals, Pediatric Plans, and Pediatric Assessments before product approval.

Complete the section(s) of this template that are relevant to your *current submission*.

Definitions:

Deferral – A deferral is granted when a pediatric assessment is required but has not been completed at the time the New Drug Application (NDA), Biologics License Application (BLA), or supplemental NDA or BLA is ready for approval. On its own initiative or at the request of an applicant, FDA may defer the submission of some or all required pediatric studies until a specified date after approval of the drug or issuance of the license for a biological product if the Agency finds that the drug or biological product is ready for approval in adults before the pediatric studies are completed, the pediatric studies should be delayed until additional safety and effectiveness data have been collected, or there is another appropriate reason for deferral.

Full Waiver – On its own initiative or at the request of an applicant, FDA may waive the requirement for a pediatric assessment for all pediatric age groups if: (1) studies would be impossible or highly impracticable; (2) there is evidence strongly suggesting that the product would be ineffective or unsafe in all pediatric age groups; or (3) the product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients, AND is not likely to be used in a substantial number of pediatric patients. If studies are being waived because there is evidence that the product would be ineffective or unsafe in all pediatric age groups, this information **MUST** be included in the pediatric use section of labeling.

Partial Waiver – FDA may waive the requirement for a pediatric assessment for a specific pediatric age group if any of the criteria for a full waiver are met for that age group or if the applicant can demonstrate that reasonable attempts to produce a pediatric formulation for that age group have failed. If a partial waiver is granted because a pediatric formulation cannot be developed, the partial waiver will only cover the pediatric groups requiring that formulation.

Pediatric Assessment – The pediatric assessment contains data gathered from pediatric studies using appropriate formulations for each age group for which the assessment is required. It also includes data that are adequate to: (1) assess the safety and effectiveness of the product for the claimed indications in all relevant pediatric subpopulations; and (2) support dosing and administration for each pediatric subpopulation for which the data support a finding that the product is safe and effective.

Pediatric Plan – A pediatric plan is the applicant’s statement of intent describing the planned or ongoing pediatric studies (e.g., pharmacokinetics/pharmacodynamics, safety, efficacy) that they plan to conduct or are conducting (i.e., the pediatric studies that will comprise the pediatric assessment). If necessary, the plan should address the development of an age-appropriate formulation and must contain a timeline for the completion of studies. FDA recommends that the timeline should include the dates the applicant will: (1) submit the protocol; (2) complete the studies; and 3) submit the study reports.

Pediatric Population/Patient- 21 CFR 201.57 defines pediatric population (s) and pediatric patient (s) as the pediatric age group, from birth to 16 years, including age groups often called neonates, infants, children, and adolescents.

PREA Pediatric Record/Pediatric Page – The pediatric record is completed for all NDAs, BLAs, or supplemental NDAs or BLAs. This record indicates whether the application triggers the Pediatric Research Equity Act (PREA), and if so, indicates how pediatric studies will be or have been addressed for each pediatric age group. If the Agency is waiving or deferring any or all pediatric studies, the pediatric record also includes the reason(s) for the waiver and/or deferral. (Note that with the implementation of DARRTS, the Pediatric Record is replacing the Pediatric Page for NDAs. The Pediatric Page is still to be used for BLAs.) For NDAs, the information should be entered into DARRTS and then the form should be created and submitted along with other required PeRC materials. Divisions should complete the Pediatric Page for NDAs that do not trigger PREA and submit the Pediatric Page via email to CDER PMHS until further notice.

Pediatric Research Equity Act (PREA) Waiver Request, Deferral Request/Pediatric Plan and Assessment Template(s)

BACKGROUND

Please check all that apply: Full Waiver Partial Waiver Pediatric Assessment Deferral/Pediatric Plan

BLA/NDA#: **206229**

PRODUCT PROPRIETARY NAME: TBD
Releasing Intrauterine System

ESTABLISHED/GENERIC NAME: Levonorgestrel

APPLICANT/SPONSOR: Medicines360

PREVIOUSLY APPROVED INDICATION/S:

(1) Intrauterine contraception for up to 5 years

(2) _____

(3) _____

(4) _____

PROPOSED INDICATION/S:

(1) Intrauterine contraception for up to 3 years

(2) _____

(3) _____

(4) _____

BLA/NDA STAMP DATE: April 30, 2014

PDUFA GOAL DATE: February 28, 2015

SUPPLEMENT TYPE:

SUPPLEMENT NUMBER:

Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

NEW *active ingredient(s) (includes new combination);* *indication(s);* *dosage form;* *dosing regimen;* or *route of administration?*

Did the sponsor submit an Agreed iPSP? Yes *No*

Did FDA confirm its agreement to the sponsor's Agreed iPSP? Yes *No*

Has the sponsor submitted a Proposed Pediatric Study Request (PPSR) or does the Division believe there is an additional public health benefit to issuing a Written Request for this product, even if the plan is to grant a waiver for this indication? (Please note, Written Requests may include approved and unapproved indications and may apply to the entire moiety, not just this product.)

Yes *No*

Is this application in response to a PREA (Postmarketing Requirement) PMR? Yes *No*

If Yes, PMR # _____ NDA # _____

Does the division agree that this is a complete response to the PMR? Yes *No*

If Yes, to either question Please complete the Pediatric Assessment Template.

If No, complete all appropriate portions of the template, including the assessment template if the division believes this application constitutes an assessment for any particular age group.

WAIVER REQUEST

Please attach:

- Draft Labeling (If Waiving for Safety and/or Efficacy) from the sponsor unless the Division plans to change. If changing the sponsor's proposed language, include the appropriate language under Question 4 in this form.*
- Pediatric Record*

1. Pediatric age group(s) to be waived. **Ages 0-12 should be waived as condition does not exist in this population**

2. Reason(s) for waiving pediatric assessment requirements (*Choose one. If there are different reasons for different age groups or indications, please choose the appropriate reason for each age group or indication. This section should reflect the Division's thinking.*)

- Studies are impossible or highly impractical (e.g. the number of pediatric patients is so small or is geographically dispersed). (Please note that in the DARRTS record, this reason is captured as "Not Feasible.") If applicable, chose from the adult-related conditions on the next page.
- The product would be ineffective and/or unsafe in one or more of the pediatric group(s) for which a waiver is being requested. Note: If this is the reason the studies are being waived, this information **MUST** be included in the pediatric use section of labeling. Please provide the draft language you intend to include in the label. The language must be included in section 8.4 and describe the safety or efficacy concerns in detail.
- The product fails to represent a meaningful therapeutic benefit over existing therapies for pediatric patients **and** is unlikely to be used in a substantial number of all pediatric age groups or the pediatric age group(s) for which a waiver is being requested.
- Reasonable attempts to produce a pediatric formulation for one or more of the pediatric age group(s) for which the waiver is being requested have failed. (Provide documentation from Sponsor) Note: Sponsor must provide data to support this claim for review by the Division, and this data will be publicly posted. (***This reason is for Partial Waivers Only***)

3. *Provide justification for Waiver:*

3. *Provide language Review Division is proposing for Section 8.4 of the label if different from sponsor's proposed language:*

Efficacy is expected to be the same for postpubertal females under the age of 18 as for users 18 years and older. Use of this product before menarche is not indicated.

Adult-Related Conditions that qualify for a waiver because they rarely or never occur in pediatrics

These conditions qualify for waiver because studies would be impossible or highly impractical.

actinic keratosis

adjunctive treatment of major depressive disorder

age-related macular degeneration

Alzheimer's disease

amyloidosis

amyotrophic lateral sclerosis

androgenic alopecia

atherosclerotic cardiovascular disease

autosomal dominant polycystic kidney disease (ADPKD)

benign monoclonal gammopathy

benign prostatic hyperplasia

cancer:

 basal cell and squamous cell skin cancer

 bladder

 breast

 cervical

 colorectal

 endometrial

 esophageal

cancer (continued):

 follicular lymphoma

 gastric

 hairy cell leukemia

 hepatocellular

 indolent non-Hodgkin lymphoma

 lung (small & non-small cell)

 multiple myeloma

 oropharynx (squamous cell)

 ovarian (non-germ cell)

 pancreatic

 prostate

 refractory advanced melanoma

 renal cell

 uterine

chronic lymphocytic leukemia

chronic obstructive pulmonary disease

cryoglobulinemia

diabetic peripheral neuropathy / macular edema

digestive disorders (gallstones)
dry eye syndrome (keratoconjunctivitis sicca)
erectile dysfunction
essential thrombocytosis
Huntington's chorea
infertility & reproductive technology
ischemic vascular diseases, such as angina, myocardial infarction, and ischemic stroke
memory loss
menopause and perimenopausal disorders
mesothelioma
myelodysplasia
myelofibrosis & myeloproliferative disorders
osteoarthritis
overactive bladder
Parkinson's disease
paroxysmal nocturnal hemoglobinuria
plasma cells and antibody production disorders
polycythemia vera
postmenopausal osteoporosis
prevention of stroke and systemic embolic events in atrial fibrillation

psoriatic arthritis
reduction of thrombotic cardiovascular events in patients with coronary artery disease
replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone
retinal vein occlusions
stress urinary incontinence
temporary improvement in the appearance of caudal lines
treatment of incompetent great saphenous veins and varicosities
type 2 diabetic nephropathy
vascular dementia/vascular cognitive disorder/impairment

DEFERRAL REQUEST

Please attach:

Pediatric Record

- 1. Age groups included in the deferral request:**
- 2. Where deferral is only requested for certain age groups, reason(s) for not including entire pediatric population in deferral request:**
- 3. Reason/s for requesting deferral of pediatric studies in pediatric patients with disease: (*Choose one. If there are different reasons for different age groups or indications, please choose the appropriate reason for each age group or indication. This section should reflect the Division's thinking.*)**
 - a. Adult studies are completed and ready for approval
 - b. Additional safety or effectiveness data needed (**describe**)
 - c. Other (**specify**)
- 4. Provide projected date for the submission of the pediatric assessment (deferral date):**
- 5. Did applicant provide certification of grounds for deferring assessments?** Yes No
- 6. Did applicant provide evidence that studies will be done with due diligence and at the earliest possible time?** Yes No

SPONSOR'S PROPOSED PEDIATRIC PLAN

- 1. Has a pediatric plan been submitted to the Agency?** Yes No
- 2. Does the division agree with the sponsor's plan?** Yes No
- 3. Did the sponsor submit a timeline for the completion of studies (must include at least dates for protocol submission, study completion and studies submitted)?** Yes No

- a. **Protocol Submission:**
- b. **Study Completion:**
- c. **Study Submission:**

4. **Has a Written Request been issued?** Yes No (If yes and the WR matches the proposed pediatric plan, please attach a copy. It is not necessary to complete the remainder of this document)
5. **Has a PPSR been submitted?** Yes No (If yes, you may submit a draft WR and have PeRC review WR and deferral/plan at the same time.)

Please note that the remainder of this section should be completed based on what the Division is requiring regardless of what the sponsor is proposing.

DIVISION'S PROPOSED PK, SAFETY, AND EFFICACY TRIAL

Please complete as much of the information below as possible. Please note that the portions of the document that are shaded are not required for early stage pediatric plans but are useful if available.

Types of Studies/Study Design:

Nonclinical Studies:

Clinical Studies:

Age group and population (indication) in which study will be performed:

This section should list the age group and population exactly as it is in the plan.

Example:

Study 1: patients aged X to Y years.

Study 2: sufficient number of subjects to adequately characterize the pharmacokinetics in the above age groups.

Number of patients to be studied or power of study to be achieved:

Example:

Study 1: X subjects in each treatment arm and be powered to show that (drug name, concentration, form etc) DRUG is not inferior to the active comparator. 50% must be females and 25% must be less than 3 years.

Study 2: This study is powered and structured to detect a 30% change in (drug name, concentration, form etc) DRUG clearance and other relevant pharmacokinetic parameters.

Entry criteria:

This section should list pertinent inclusion/exclusion criteria.

Example:

*Entry criteria: Pediatric patients with disease x diagnosed with laboratory test of LFTs
Patients must have a negative pregnancy test if female..*

Clinical endpoints:

Example:

Study 1: Clinical outcome and safety will be the primary endpoints.

Study 2: The primary pharmacokinetic analysis of (drug name, concentration, form etc) DRUG should attempt to include all the patients in the study with determination of the following parameters: single dose and steady state AUC, Cmax, Tmax, and CL/F.

Timing of assessments:

Example :baseline, week 1, 4, and 6

Statistical information (statistical analyses of the data to be performed):

Example:

Study 1 non-inferiority: two-sided 95% confidence interval (CI) of treatment difference in improvement rates should be within 25% of the control's response rate.

Study 2: descriptive statistical methods for AUC, C max, Tmax, CI/F and compared to adults.

Division comments on product safety:

Are there any safety concerns currently being assessed? Yes No

Are there safety concerns that require us to review post-marketing safety data before fully designing the pediatric studies? Yes No

Will a DSMB be required? Yes No

Other comments:

Division comments on product efficacy:

Division comments on sponsor proposal to satisfy PREA:

PeRC ASSESSMENT TEMPLATE

Please attach:

- Proposed Labeling from the sponsor unless the Division plans to change. If changing the language, include the appropriate language at the end of this form.*
- Pediatric Record*

Date of PREA PMR:

Description of PREA PMR: *(Description from the PMC database is acceptable)*

Was Plan Reviewed by PeRC? **Yes** **No** If yes, did sponsor follow plan?

If studies were submitted in response to the Written Request (WR), provide the annotated WR in lieu of completing the remainder of the Pediatric Assessment template.

Indication(s) that were studied:

This section should list the indication(s) exactly as written in the *protocols*.

Example:

DRUG for the treatment of the signs and symptoms of disease x.

Number of Centers _____

Number and Names of Countries _____

Drug information:

Examples in italics

- **Route of administration:** *Oral*
- ***Formulation:** *disintegrating tablet*
- **Dosage:** *75 and 50 mg*
- **Regimen:** *list frequency of dosage administration*

**If the dosage form is powder for oral suspension; provide information on storage statement and concentration after reconstitution (e.g. with water, juice or apple sauce etc.)*

Types of Studies/ Study Design:

Example:

Study 1: Multi- center, randomized, active controlled double blind study to evaluate the safety and efficacy of (drug name, concentration, form etc) DRUG administered twice daily for the treatment of patients with disease x.

Study 2: PK and safety study of (drug name, concentration, form etc) DRUG in patients with disease x.

Age group and population in which study/ies was/were performed:

Example:

Study 1: patients aged X to Y years.

Study 2: sufficient number of patients to adequately characterize the pharmacokinetics in the above age groups.

Number of patients studied or power of study achieved:

Example:

Study 1: X patients in each treatment arm and was powered to show that (drug name, concentration, form etc) DRUG is not inferior to the active comparator. 50% were females and 25% were less than 3 years.

Study 2: powered and structured to detect a 30% change in (drug name, concentration, form etc) DRUG clearance and other relevant pharmacokinetic parameters. The study included at least X evaluable patients. .

Entry criteria:

This section should list pertinent inclusion/exclusion criteria.

Example:

Entry criteria: Pediatric patients with disease x diagnosed with laboratory test of LFTs

Patients had a negative pregnancy test if female.

Clinical endpoints:

Example:

Study 1: Clinical outcome and safety were the primary endpoints.

Study 2: The primary pharmacokinetic analysis of (drug name, concentration, form etc) DRUG attempted to include all the patients in the study with determination of the following parameters: single dose and steady state AUC, Cmax, Tmax, and CL/F

Statistical information (statistical analyses of the data performed):

This section should list the statistical tests conducted.

Example:

Study 1 - two-sided 95% confidence interval (CI) of treatment difference in improvement rates were within 25% of the control's response rate.

Study 2: descriptive statistical methods for AUC, C max, Tmax, Cl/F and compared to adults.

Timing of assessments:

Example:

Baseline, week 2, week, 6, and end of treatment

Division comments and conclusions (Summary of Safety and Efficacy)

Provide language Review Division is proposing for the appropriate sections of the label if different from sponsor-proposed language.

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

/s/

ZETA-MAE C WILLIAMSON
11/17/2014

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 206229 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: Liletta IUS Established/Proper Name: levonorgestrel Dosage Form: IUS		Applicant: Medicine360 Agent for Applicant (if applicable):
RPM: Z. Charlene Williamson		Division: Bone, Reproductive, and Urologic Products
NDA Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) BLA Application Type: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a) Efficacy Supplement: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a)	<p style="margin: 0;"><u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u></p> <ul style="list-style-type: none"> Review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) <p style="margin-left: 20px;"> <input checked="" type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity (<i>notify CDER OND IO</i>) Date of check: </p> <p style="margin-left: 20px;"><i>Note: 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.</i></p>	
❖ Actions		
<ul style="list-style-type: none"> Proposed action User Fee Goal Date is <u>February 27, 2015</u> 		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> Previous actions (<i>specify type and date for each action taken</i>) 		<input checked="" type="checkbox"/> None
❖ 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 _____		<input type="checkbox"/> Received
❖ Application Characteristics ³		

¹ The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.

² For resubmissions, 505(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., new listed drug, patent certification revised).

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.

Review priority: Standard Priority
 Chemical classification (new NDAs only):
 (*confirm chemical classification at time of approval*)

- | | |
|---|---|
| <input type="checkbox"/> Fast Track | <input type="checkbox"/> Rx-to-OTC full switch |
| <input type="checkbox"/> Rolling Review | <input type="checkbox"/> Rx-to-OTC partial switch |
| <input type="checkbox"/> Orphan drug designation | <input type="checkbox"/> Direct-to-OTC |
| <input type="checkbox"/> Breakthrough Therapy designation | |

NDAs: Subpart H

- Accelerated approval (21 CFR 314.510)
 Restricted distribution (21 CFR 314.520)

Subpart I

- 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

BLAs: Subpart E

- Accelerated approval (21 CFR 601.41)
 Restricted distribution (21 CFR 601.42)

Subpart H

- Approval based on animal studies

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

Comments:

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications (<i>approvals only</i>)	
• Office of Executive Programs (OEP) liaison has been notified of action	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• Indicate what types (if any) of information were issued	<input checked="" type="checkbox"/> None <input type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
CONTENTS OF ACTION PACKAGE	
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included

Action Letters	
❖ Copies of all action letters <i>(including approval letter with final labeling)</i>	Action(s) and date(s) AP - February 26, 2015
Labeling	
❖ Package Insert <i>(write submission/communication date at upper right of first page of PI)</i>	
<ul style="list-style-type: none"> • Most recent draft labeling <i>(if it is division-proposed labeling, it should be in track-changes format)</i> 	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	<input checked="" type="checkbox"/> Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling <i>(write submission/communication date at upper right of first page of each piece)</i>	<input type="checkbox"/> Medication Guide <input checked="" type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
<ul style="list-style-type: none"> • Most-recent draft labeling <i>(if it is division-proposed labeling, it should be in track-changes format)</i> 	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	<input checked="" type="checkbox"/> Included
❖ Labels (full color carton and immediate-container labels) <i>(write submission/communication date on upper right of first page of each submission)</i>	
<ul style="list-style-type: none"> • Most-recent draft labeling 	<input checked="" type="checkbox"/> Included
❖ Proprietary Name <ul style="list-style-type: none"> • Acceptability/non-acceptability letter(s) <i>(indicate date(s))</i> • Review(s) <i>(indicate date(s))</i> 	12/04/2014 12/03/2014
❖ Labeling reviews <i>(indicate dates of reviews)</i>	RPM: <input checked="" type="checkbox"/> 06.25.2014 DMEPA: <input checked="" type="checkbox"/> 11.05.2014 DMPP/PLT (DRISK): <input checked="" type="checkbox"/> 01.30.2015 OPDP: <input checked="" type="checkbox"/> 01.29.2015 SEALD: <input checked="" type="checkbox"/> None CSS: <input type="checkbox"/> None Other: <input type="checkbox"/> None
Administrative / Regulatory Documents	
❖ RPM Filing Review ⁴ /Memo of Filing Meeting <i>(indicate date of each review)</i>	07.14.2014
❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	<input type="checkbox"/> Not a (b)(2) 02.26.2015
❖ NDAs only: Exclusivity Summary <i>(signed by Division Director)</i>	<input checked="" type="checkbox"/> Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
<ul style="list-style-type: none"> • Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

⁴ Filing reviews for scientific disciplines are NOT required to be included in the action package.

<ul style="list-style-type: none"> This application is on the AIP <ul style="list-style-type: none"> If yes, Center Director's Exception for Review memo (<i>indicate date</i>) If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Not an AP action
❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> Date reviewed by PeRC _____ If PeRC review not necessary, explain: _____ 	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, etc.) (<i>do not include previous action letters, as these are located elsewhere in package</i>)	05.14.201;07.14.2014;08.12.2014;11.05.2014;11.10.2014(2);12.04.2014;01.02.2015; 01.07.2015; 01.28.2015;02.03.2015 (2); 02.04.2015;02.26.2015
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	
❖ Minutes of Meetings <ul style="list-style-type: none"> If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>) Pre-NDA/BLA meeting (<i>indicate date of mtg</i>) EOP2 meeting (<i>indicate date of mtg</i>) Mid-cycle Communication (<i>indicate date of mtg</i>) Late-cycle Meeting (<i>indicate date of mtg</i>) Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>) 	<input checked="" type="checkbox"/> N/A or no mtg <input type="checkbox"/> No mtg 09.17.2013 <input checked="" type="checkbox"/> No mtg <input checked="" type="checkbox"/> N/A <input checked="" type="checkbox"/> N/A
❖ Advisory Committee Meeting(s) <ul style="list-style-type: none"> Date(s) of Meeting(s) 	<input checked="" type="checkbox"/> No AC meeting
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Division Director Summary Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 02.26.2015
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 02.25.2015
PMR/PMC Development Templates (<i>indicate total number</i>)	<input type="checkbox"/> None 02.26.2015
Clinical	
❖ Clinical Reviews <ul style="list-style-type: none"> Clinical Team Leader Review(s) (<i>indicate date for each review</i>) Clinical review(s) (<i>indicate date for each review</i>) Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>) 	<input checked="" type="checkbox"/> No separate review 02.23.2015 <input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not (<i>indicate date of review/memo</i>)	See Clinical Review Page 19
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> None

❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> N/A
❖ Risk Management <ul style="list-style-type: none"> REMS Documents and REMS Supporting Document (<i>indicate date(s) of submission(s)</i>) REMS Memo(s) and letter(s) (<i>indicate date(s)</i>) Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>) 	<input checked="" type="checkbox"/> None
❖ OSI Clinical Inspection Review Summary(ies) (<i>include copies of OSI letters to investigators</i>)	<input type="checkbox"/> None requested 12.15.2014;01.07.2015(2);
Clinical Microbiology <input type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 01.23.2015
Biostatistics <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
Statistical Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 02.23.2015
Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 01.30.2015
❖ OSI Clinical Pharmacology Inspection Review Summary (<i>include copies of OSI letters</i>)	<input checked="" type="checkbox"/> None requested
Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
• Supervisory Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
• Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	<input type="checkbox"/> None 12.10.204 (2); 02.11.2015;
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary (<i>include copies of OSI letters</i>)	<input checked="" type="checkbox"/> None requested

Product Quality <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review
• Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i>	<input type="checkbox"/> None 02.26.2015;02.11.2015;12.19.2014
❖ Microbiology Reviews	<input type="checkbox"/> Not needed 01.23.2015
<input checked="" type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i>	
<input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) <i>(indicate date of each review)</i>	
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i>	<input type="checkbox"/> None CDRH: 02.02.2015; 01.28.2015
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>	05/30/2014
<input type="checkbox"/> Review & FONSI <i>(indicate date of review)</i>	
<input type="checkbox"/> Review & Environmental Impact Statement <i>(indicate date of each review)</i>	
❖ Facilities Review/Inspection	
<input type="checkbox"/> NDAs: Facilities inspections (include EER printout or EER Summary Report only; do NOT include EER Detailed Report; date completed must be within 2 years of action date) <i>(only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites⁵)</i>	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER (date of most recent TB-EER must be within 30 days of action date) <i>(original and supplemental BLAs)</i>	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation <i>(check box only, do not include documents)</i>	Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input checked="" type="checkbox"/> Not needed (per review)

⁵ 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.

Day of Approval Activities	
❖ For all 505(b)(2) applications: <ul style="list-style-type: none"> • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) 	<input checked="" type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity (<i>Notify CDER OND IO</i>)
<ul style="list-style-type: none"> • Finalize 505(b)(2) assessment 	<input checked="" type="checkbox"/> Done
❖ For Breakthrough Therapy(BT) Designated drugs: <ul style="list-style-type: none"> • Notify the CDER BT Program Manager 	<input type="checkbox"/> Done (<i>Send email to CDER OND IO</i>)
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	<input checked="" type="checkbox"/> Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	<input checked="" type="checkbox"/> Done
❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name	<input type="checkbox"/> Done
❖ Ensure Pediatric Record is accurate	<input checked="" type="checkbox"/> Done
❖ Send approval email within one business day to CDER-APPROVALS	<input checked="" type="checkbox"/> Done

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/s/

ZETA-MAE C WILLIAMSON
03/17/2015



NDA 206229

LABELING PMR/PMC DISCUSSION COMMENTS

Medicines360
Attention: Victoria Hale, Ph.D.
Chief Executive Officer and Founder
353 Sacramento Street, Suite 900
San Francisco, CA 94111

Dear Dr. Hale:

Please refer to your New Drug Application (NDA) dated April 29, 2014, received April 30, 2014, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for levonorgestrel-releasing intrauterine system (IUS), 52 mg.

We also refer to our July 14, 2014 letter in which we notified you of our target date of February 1, 2015, for communicating labeling changes and/or postmarketing requirements/commitments in accordance with the "PDUFA Reauthorization Performance Goals and Procedures - Fiscal Years 2013 Through 2017."

On February 2, 2015, you were in receipt of our proposed labeling revisions. We request that you resubmit labeling by February 9, 2015. The resubmitted labeling will be used for further labeling discussions.

Your proposed prescribing information (PI) must conform to the content and format regulations found at [CFR 201.56\(a\) and \(d\)](#) and [201.57](#). Prior to resubmitting your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

We request that you commit to completing a Postmarketing Commitment to provide further data on the functionality of the THI-002 inserter with Liletta. Our rationale and some details of the requested study follow.

Study L104 was conducted at 6 sites that are known to be experienced with IUS insertions and associated adverse events. Although the study was conducted as we requested, it provided a limited evaluation of the functionality of the THI-002 inserter, because it enrolled a relatively small number of women (100), and had only 24 hour follow-up in person and then a follow up phone call about 7 days post-insertion to assess any further adverse events.

We note the following findings from Study L104 regarding the THI-002 inserter:

- The “successful insertion” rate was 99% (95% on the first attempt)
- However, 19 insertions were rated as “difficult”
- After sounding the uterine cavity, there was difficulty passing the inserter through the cervical canal in 13 cases, with problems including “kinking” of the inserter tube and problems with the flexibility of the tube
- There was recurrent difficulty loading the IUS into the inserter in 4 cases
- In 4 cases, the IUS pulled out when the inserter was withdrawn

Therefore, while we believe that Study L104 supports the overall safety and usability of the THI-002 inserter, there is a need for additional information about the performance of the THI-002 inserter that should be collected post-approval. A program modeled after the European AMPS study for Levosert (LNG-IUS) is requested, to focus on the following data:

- characterizing ease of insertion, insertion difficulties, and failed insertions
 - use of local anesthesia
 - use of rigid dilation
 - use of ultrasound guidance
- adverse events (AEs) such as pain, vasovagal events, excessive bleeding and uterine perforation during insertion and before the subject leaves the healthcare facility after insertion
- subsequent AEs such as pain and bleeding in the 7-14 days after IUS placement
- any additional AEs reported at the follow-up visit
- expulsions, infections, and other more serious AEs that may be delayed but related to the insertion procedure or IUS

Similar to the AMPS study, approximately 1,000 women should be studied from a variety of clinical settings (private practice, family planning clinics, and teaching institutions). The enrolled subjects should be followed for a minimum of three months to monitor for expulsion, perforation and infection because these two adverse events are more common during this time period and may be related to the inserter or the insertion process. IUS removal data is not of primary importance and does not need to be obtained unless the IUS was removed specifically due to an insertion-related AE. Data on the utilization pattern of Liletta is also not required.

We also request that the study enroll representative proportions of nulliparous users and obese women to reflect the overall user population for the labeled indication. In addition, for women who have the IUS inserted post-partum, data should be collected on time since delivery/pregnancy termination, and on whether they are lactating.

We propose the following milestones for this PMC:

Final Protocol Submission: 2/28/2016
Study/Trial Completion: 2/28/18
Final Report Submission: 2/28/19

However, we encourage you to submit the protocol well in advance of this milestone date, to allow time for review by the Division and possible modification in accord with FDA comments.

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

Sincerely,

{See appended electronic signature page}

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

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/s/

ZETA-MAE C WILLIAMSON
02/04/2015

From: [Williamson, Charlene](#)
To: [Andrea Olariu \(aolariu@medicines360.org\)](mailto:aolariu@medicines360.org)
Cc: [Williamson, Charlene](#)
Subject: NDA 206229 - Liletta Labeling
Date: Monday, February 02, 2015 12:52:40 PM
Attachments: [Liletta PI TO SPONSOR 02.02.2015.doc](#)
[Liletta PPI TO SPONSOR 02.01.2015.doc](#)

Andrea,

Attached is the labeling for Liletta. Please review the Division's recommendations/changes and respond in track changes by Friday COB, February 6, 2015.

Please acknowledge receipt of this email.

Also, Your labeling indicates: "LILETTA is MR safe. It is safe to have a MRI following LILETTA insertion." The standard MRI safety term from ASTM F2503 is "MR Safe," where the "S" in "Safe" is a capital letter. Please use the term MR Safe in your labeling.

Please acknowledge receipt of this email.

Thanks
Charlene

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/s/

ZETA-MAE C WILLIAMSON
02/03/2015

From: [Williamson, Charlene](#)
To: [Andrea Olariu \(aolariu@medicines360.org\)](mailto:aolariu@medicines360.org)
Cc: [Williamson, Charlene](#)
Subject: NDA 206229 - Information Request
Date: Friday, January 30, 2015 1:40:55 PM

Andrea,

Another information request. Please respond by February 5, 2015.

- 1) Clarify whether the initial cycle of Liletta use, in which subjects may have used an additional method of contraception, was included in the denominator of the Pearl Index (PI) calculation as at-risk cycles. If they were, we do not agree with this, and request that you recalculate the Year 1 and cumulative 3-year PIs excluding such cycles. Initial cycles for subjects who did NOT use another method of calculation may be retained in the denominator.
- 2) Also, in this calculation, add in all additional pregnancies (including ectopics) reported in the safety update to the calculation for the respective year and cumulative PI.
- 3) Submit an updated analysis dataset with corrected cycles and pregnancy information.
- 4) Provide new calculations for the ectopic pregnancy rate and the IUS expulsion rate as cases were added with the safety update.

Please acknowledge receipt.

Thanks
Charlene

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/s/

ZETA-MAE C WILLIAMSON
02/03/2015

From: [Andrea Olariu](#)
To: [Williamson, Charlene](#)
Subject: RE: NDA 206229 - Another Information Request 01.28.2015
Date: Wednesday, January 28, 2015 1:09:42 PM

Charlene,
I confirm that the device inserted in the uterus has no metal in its composition. Please let me know if my response by e-mail is sufficient.
Thank you,
Andrea

Andrea Olariu
General Manager, Vice President Clinical Affairs
Main: 415.951.8700 | Direct: (b) (4) | Fax: 415.951.8701
aolariu@medicines360.org

Medicines360 | 353 Sacramento St | Suite 900 | San Francisco, CA 94111
www.medicines360.org



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From: Williamson, Charlene [mailto:Charlene.Williamson@fda.hhs.gov]
Sent: Wednesday, January 28, 2015 8:05 AM
To: Andrea Olariu
Cc: Williamson, Charlene
Subject: NDA 206229 - Another Information Request 01.28.2015

Andrea,

Please provide us with the following ASAP:

The patient leaflet indicates that the device is composed of plastic. Can you confirm that it's composed entirely of plastic? Is there any metal at all, even the tiniest amount?

Please acknowledge receipt.

I need a response almost momentarily.

Charlene

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/s/

ZETA-MAE C WILLIAMSON
01/28/2015

From: [Williamson, Charlene](#)
To: [Andrea Olariu \(adolariu@medicines360.org\)](mailto:adolariu@medicines360.org)
Cc: [Williamson, Charlene](#)
Subject: NDA 206229 - Liletta Information Request
Date: Wednesday, January 07, 2015 8:09:19 AM

Andrea,

An additional information request:

Carton and Container Labeling:

Please update the carton labeling with the following statement:

- “ See package insert (b) (4)”

MRI compatibility in Labeling

Provide below is the link to the guidance on how you should most appropriately categorize your product.

<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm107708.pdf>

Please acknowledge receipt of this email.

Thanks

Charlene

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/s/

ZETA-MAE C WILLIAMSON
01/07/2015

**PeRC PREA Subcommittee Meeting Minutes
December 3, 2014**

PeRC Members Attending:

Wiley Chambers

George Greeley

Kevin Krudys

Dionna Green

Dianne Murphy

Kristiana Brugger

Colleen LoCicero

Julia Pinto

Greg Reaman NON RESPONSIVE)

Hari Cheryl Sachs

Michelle Roth-Cline

Karen Davis-Bruno

Peter Starke

Olivia Ziolkowski

Rosemary Addy

Barbara Buch

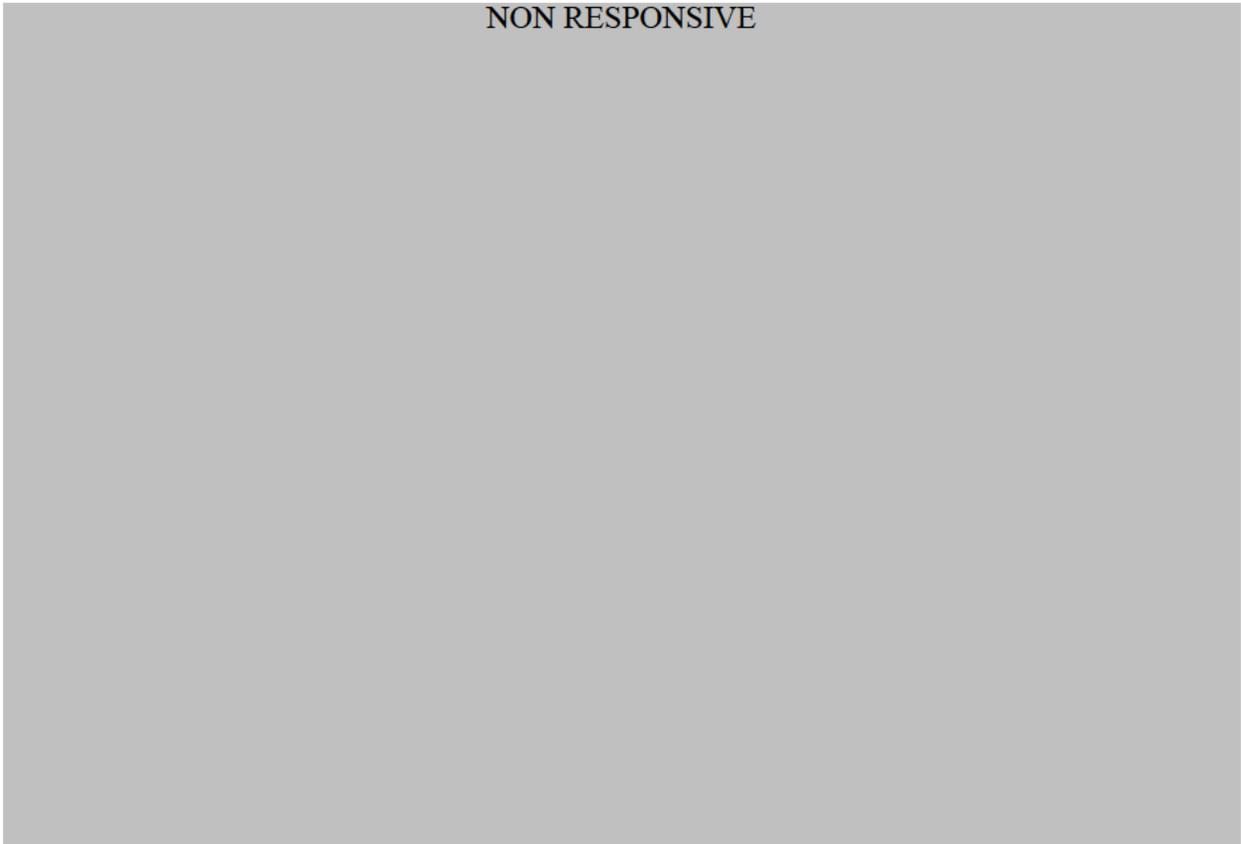
Nisha Jain NON RESPONSIVE

Adrienne Hornatko-Munoz NON RESPONSIVE

PREA

10:50	NDA	NON RESPONSIVE		
11:10	BLA			
11:20	NDA			
11:30	NDA			
11:40	NDA			
	<i>NDA</i>	<i>206229</i>	<i>(b) (4) (Partial Waiver/Extrapolation)</i>	<i>Intrauterine contraception for up to 3 years</i>
	<i>NDA</i>	NON RESPONSIVE		
	<i>NDA</i>			

NON RESPONSIVE



2 Page(s) has been Withheld in Full as NON-RESPONSIVE immediately following this page

^{(b) (4)} **Partial Waiver/Extrapolation**

- Proposed Indication: Intrauterine contraception for up to 3 years
- This application triggered PREA as a new indication.
- The PDUFA goal date is January 30, 2015.
- The Division clarified
- *PeRC Recommendations:*
 - The PeRC agreed with the partial waiver and assessment presented in all pediatric patients for this product.

“NON RESPONSIVE”

"NON RESPONSIVE"

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/s/

GEORGE E GREELEY
12/22/2014



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 206229

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Medicines360
353 Sacramento Street, Suite 900
San Francisco, CA 94111

ATTENTION: Victoria Hale, PhD
CEO and Founder

Dear Dr. Hale:

Please refer to your New Drug Application (NDA), dated April 29, 2014, and received, April 30, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Levonorgestrel-releasing Intrauterine System, 52 mg.

We also refer to your correspondence, dated October 2, 2014, and received, October 3, 2014, requesting review of your proposed proprietary name, Liletta.

We have completed our review of the proposed proprietary name, Liletta and have concluded that it is acceptable.

If any of the proposed product characteristics as stated in your October 2, 2014, 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 Shawnetta Jackson, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-4952. For any other information regarding this application, contact Charlene Williamson, Regulatory Project Manager in the Office of New Drugs, at (301) 796-1025.

Sincerely,

{See appended electronic signature page}

Kellie A. Taylor, Pharm.D., MPH
Deputy Director
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

TODD D BRIDGES on behalf of KELLIE A TAYLOR
12/04/2014

Andrea,

The CMC Reviewer has an additional information request regarding your NDA submission. Please respond by December 1, 2014.

1. Add the proposed detailed description to the DP Specification. It is noted that (b) (4) is the proposed acceptance criterion for appearance testing. A detailed description is needed to include in the specification. Add the following detailed description to the acceptance criterion for appearance testing: (b) (4)
(b) (4)
(b) (4)
(b) (4)
(b) (4)
2. It is noted that a unique math model (b) (4) to derive the accuracy result (b) (4) was used in the HPLC method validation study. However, there were a few set of data missing in the validation report. Thus, provide Annex A and B for both reports: DT-QC-014: "Validation report for the LC determination of levonorgestrel related substances in (b) (4) IUD" and "Validation report for the LC determination of levonorgestrel in (b) (4) IUD".

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/s/

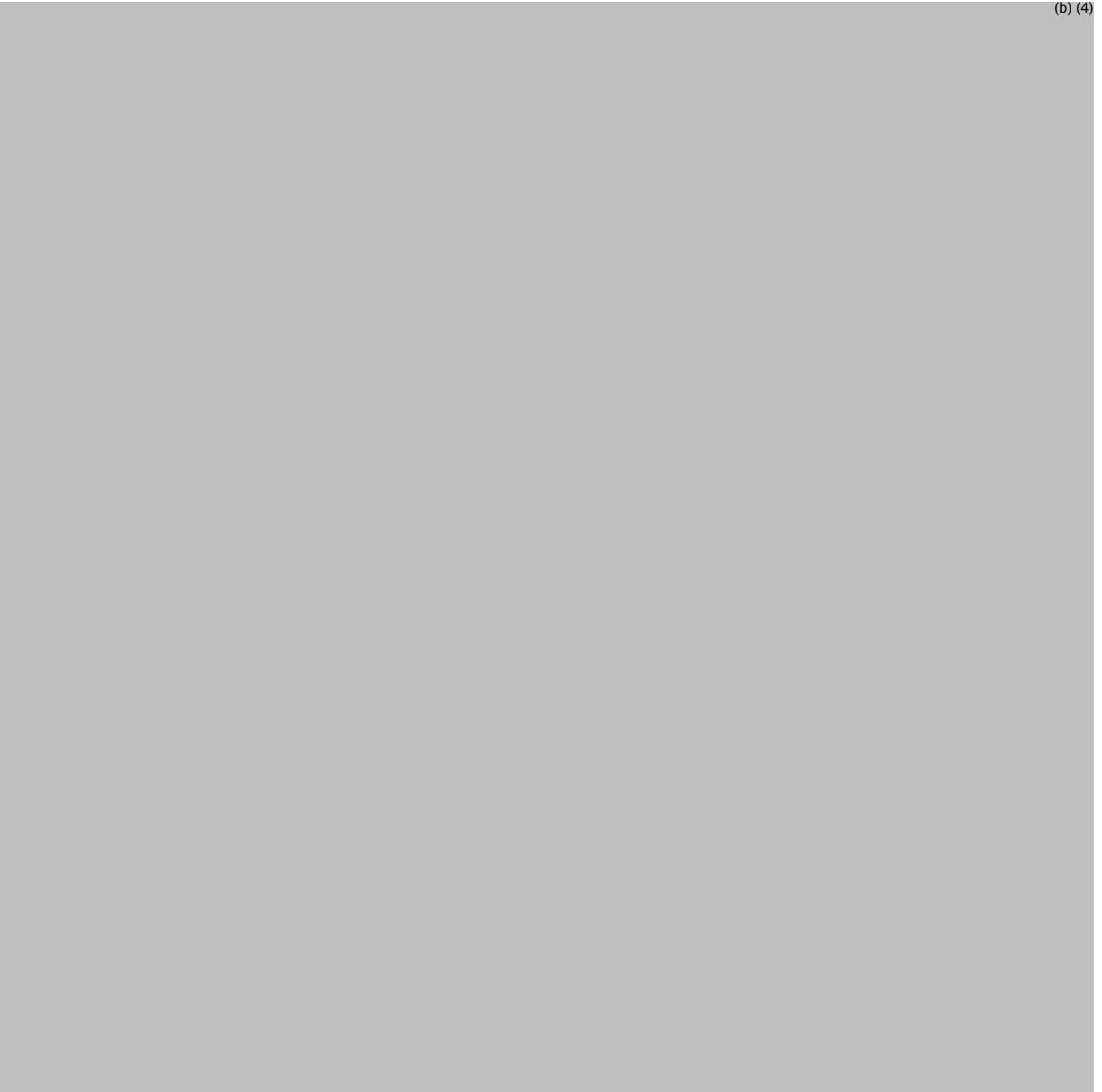
ZETA-MAE C WILLIAMSON
11/10/2014

Address the following deficiencies and respond by December 1, 2014:

1. The specification for the frictional force necessary to move the flange along the inserter tube has been modified as a result of the early findings of the stability study. As part of the justification for the change in the specification, you have provided a detailed discussion of the information used to initially set the specification. What was not included in this discussion was any reference to the frictional force of the THI-001 (b) (4)



2. (b) (4)



3.

4.

5.

6.



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/s/

ZETA-MAE C WILLIAMSON
11/10/2014

Williamson, Charlene

From: Williamson, Charlene
Sent: Wednesday, November 05, 2014 11:27 AM
To: Williamson, Charlene
Subject: FW: NDA 206229 Information Request (NEEDS DARRTS)

From: Williamson, Charlene
Sent: Wednesday, November 05, 2014 10:27 AM
To: Andrea Olariu (aolariu@medicines360.org)
Cc: Williamson, Charlene
Subject: NDA 206229 Information Request (NEEDS DARRTS)

Andrea,

Please acknowledge receipt and respond to the below request regarding the in vitro drug release data:

Provide in vitro drug release data at time 0 (i.e. before the batches are placed at long-term stability conditions) for as many of your clinical and stability batches as possible using your proposed in vitro release method. Ensure that you include the complete release data (i.e. individual, mean, standard deviation, and profiles) for each batch tested.

We request this information by COB December 1, 2014.

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/s/

ZETA-MAE C WILLIAMSON
11/05/2014



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 206229

**PROPRIETARY NAME REQUEST
UNACCEPTABLE**

Medicines360
353 Sacramento Street, Suite 900
San Francisco, CA 94111

ATTENTION: Victoria Hale, PhD
CEO and Founder

Dear Dr. Hale:

Please refer to your New Drug Application (NDA) dated April 29, 2014, and received April 30, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Levonorgestrel-releasing Intrauterine (b)(4), 52 mg.

We also refer to your correspondence, dated May 19, 2014, and received May 20, 2014, requesting review of your proposed proprietary name, (b)(4)

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

(b)(4)

We note that you have not proposed an alternate proprietary name for review. If you intend to have a proprietary name for this product, we recommend that you submit a new request for a proposed proprietary name review. (See the Guidance for Industry, *Contents of a Complete Submission for the Evaluation of Proprietary Names*, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf> and “PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2008 through 2012”.)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Shawnetta Jackson, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796- 4952. For any other information regarding this application, contact Charlene Williamson, Regulatory Project Manager in the Office of New Drugs, at (301) 796-1025.

Sincerely,

{See appended electronic signature page}

Kellie A. Taylor, Pharm.D., MPH
Deputy Director
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

KELLIE A TAYLOR
08/12/2014



NDA 206229

**FILING COMMUNICATION –
NO FILING REVIEW ISSUES IDENTIFIED**

Medicines360
Attention: Victoria Hale, Ph.D.
Chief Executive Officer and Founder
353 Sacramento Street, Suite 900
San Francisco, CA 94111

Dear Dr. Hale:

Please refer to your New Drug Application (NDA) dated April 29, 2014, received April 30, 2014, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for levonorgestrel-releasing intrauterine system (IUS), 52 mg.

We also refer to your amendments dated May 19, 20, and 29, 2014.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is **February 28, 2015**.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests or postmarketing requirements by **February 1, 2015**.

At this time, we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. However, we have the following comments and requests:

Please submit the following information:

1. The method suitability testing to support the product sterility test could not be located in the submission. Provide either the location in the submission or submit the report to the NDA.
2. Submit drug exposure-response (e.g., secondary efficacy endpoints such as return to menses, return to fertility, and endometrial thickness) analyses for Study M360-L102, referring to the *Guidance for Industry - Exposure-Response* <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm072109.pdf>.
3. Submit the analysis assessing the effect of race on drug exposure and response (e.g., secondary efficacy endpoints such as return to menses, return to fertility, and endometrial thickness) for Study M360-L102.
4. Submit the analysis assessing the effect of race, body weight, and age on drug exposure of the IUS from the Study Levosert-20.

PRESCRIBING INFORMATION

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#). We encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances.

During our preliminary review of your submitted labeling, we have identified the following labeling issues and have the following labeling comments or questions:

Highlights

1. The Dosage Forms and Strengths section is missing.
2. Under Adverse Reactions, the dash is missing in the FDA phone number.
3. A horizontal line is missing separating the Table of Contents from the Full Prescribing Information (FPI).
4. Highlights headings need to be centered within the horizontal line.
5. Under the Indications and Usage Section, the name of established pharmacologic class (“(b)(4) intrauterine system”) is missing.

Table of Contents

1. In the Full Prescribing Information, the text “CONTENTS” is missing.

Full Prescribing Information:

1. The revision date is missing at the end of the patient labeling (21 CFR Part 208).
2. Please remove all final decimal points in your numbering system.

We request that you resubmit labeling (in Microsoft Word format) that addresses these issues by **August 1, 2014**. The resubmitted labeling will be used for further labeling discussions. Use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials and draft or mock-up form with annotated references, and the proposed PI, and patient labeling. Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Do not submit launch materials until you have received our proposed revisions to the PI and patient labeling, and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of the criteria apply at this time to your application, you are exempt from these requirements; you are exempt from these requirements. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

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.
Deputy Director
Division of Bone, Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

AUDREY L GASSMAN
07/14/2014



NDA 206229

NDA ACKNOWLEDGMENT

Medicines360
Attention: Victoria Hale, Ph.D.
Chief Executive Officer
353 Sacramento Street, Suite 900
San Francisco, CA 94111

Dear Dr. Hale:

We have received your New Drug Application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: (b) (4) (levonorgestrel releasing intrauterine system)

Date of Application: April 29, 2014

Date of Receipt: April 30, 2014

Our Reference Number: NDA 206229

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on June 29, 2014, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

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

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

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

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

Sincerely,

{See appended electronic signature page}

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

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/s/

ZETA-MAE C WILLIAMSON
05/14/2014



IND 105836

MEETING PRELIMINARY COMMENTS

Medicines360
Attention: Andrea Olariu, MD, PhD
General Manager, Vice President Clinical Affairs
353 Sacramento St, Suite 900
San Francisco, CA 94111

Dear Dr. Olariu:

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

We also refer to your June 28, 2013, correspondence, received July 1, 2013, requesting a meeting to discuss planned NDA submission.

Our preliminary responses to your meeting questions are enclosed.

You should provide, to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

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

Sincerely,

{See appended electronic signature page}

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

ENCLOSURE:
Preliminary Meeting Comments



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PRELIMINARY MEETING COMMENTS

Meeting Type: B
Meeting Category: Pre-NDA
Meeting Date and Time: September 17, 2013 – 10:00 AM – 11:30 AM
Meeting Location: 10903 New Hampshire Avenue, Bldg. 22 Room 1311
Silver Spring, MD 20903
Application Number: 105836
Product Name: levonorgestrel releasing intrauterine system
Indication: prevention of pregnancy
Sponsor/Applicant Name: Medicines360

Introduction:

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for September 17, 2013, 10:00 AM – 11:30 AM, 10903 New Hampshire Avenue, Bldg. 22 Room 1311, Silver Spring, MD 20902 between Sponsor and the Division of Bone, Reproductive and Urologic Products. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). Note that if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, we may not be prepared to discuss or reach agreement on such changes at the meeting although we will try to do so if possible. If any modifications to the development plan or additional questions for which you would like CDER feedback arise before the meeting, contact the RPM to discuss the possibility of including these items for discussion at the meeting.

BACKGROUND

Medicine 360 is developing LNG20, a levonorgestrel-releasing intrauterine system (IUS) (b) (4) and plans to seek an initial indication for the prevention of pregnancy for up to three years.

Medicine 360 has a phase 3 trial (M360-L102) ongoing to evaluate the safety and efficacy of LNG20 IUS for five years. The Division agreed that the product could potentially be approved prior to completion of this study, with the indication and labeling to reflect the actual data that are submitted. (b) (4)

The purpose of the Pre-NDA meeting is to discuss the 505(b)(2) pathway, the adequacy of the clinical, nonclinical, and chemistry, manufacturing and controls information and the acceptance of the stability data to support the filing of an NDA.

Regulatory/Medical

Question 1

Medicines360 is planning to rely on data from its own clinical study, nonclinical studies to which it has right of reference, and information from the public domain (published literature) for approval of its LNG20 IUS as described in (a) to (c) below.

- a. Medicines360 has conducted a Phase 3 clinical trial to establish safety and efficacy of its LNG20 IUS.*
- b. The safety and efficacy of levonorgestrel are well established through its long history of clinical use as a contraceptive in multiple approved products. In addition to its Phase 3 study, Medicines360 plans to rely on information for levonorgestrel in the public domain. Medicines360 does not plan to reference the approved Mirena labeling. Instead, Medicines360 plans to rely on the published literature used to support the labeling for approved levonorgestrel products; the literature reports are included in the briefing package.*
- c. In addition to the Phase 3 study, Medicines360 plans to rely on biocompatibility studies to which it has right of reference and from the published literature to satisfy the safety requirements for the T-frame, drug reservoir, membrane, removal threads, and inserter.*

Does the Division agree that the literature provided in this briefing package is adequate to supplement data from Medicines360's Phase 3 and nonclinical studies and that no listed drug is needed to support the submission, review, and potential approval of Medicines360's 505(b)(2) NDA?

FDA Response:

The Sponsor's plan to rely on data from its own studies, nonclinical studies to which it has right of reference, and published literature appears reasonable. However, reliance on published literature describing a listed drug(s) is considered to be reliance on FDA's finding of safety and/or effectiveness for the listed drug(s). The Sponsor will need to identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54.

See additional 505(b)(2) information under subsection: 505(b)(2) REGULATORY PATHWAY.

Question 2

Medicines360 is planning to provide proposed product labeling for the LNG20 IUS supported by the information from its Phase 3 clinical trial program, clinical and nonclinical information in the public domain regarding levonorgestrel, and information reflective of the FDA's draft Guidance for Industry regarding hormonal contraceptive labeling (Draft Guidance for Industry:

Labeling for Combined Oral Contraceptives [2004] (CDER, 2004) and consistent with the approved product labeling for other levonorgestrel-only products.

- 2a. Is the Division in agreement with this approach for the proposed LNG20 IUS labeling information?*
- 2b. Does the Division agree that the draft labeling content is complete and appropriately referenced with public domain information upon which Medicines360 plans to rely?*

FDA Response:

This approach is generally acceptable; however, the draft Combined Oral Contraceptive labeling guidance no longer fully reflects the Division's current thinking on labeling hormonal contraceptives. The Sponsor is encouraged to consider the format and content of other progestin-only and non-oral hormonal contraceptives labels in PLR format in developing its proposed labeling.

In addition, while recommendations about contraception from other bodies, such as the Centers for Disease Prevention and Control, are appreciated, the Division will make its own determination about the appropriate indication and target population, based on the data provided in support of the application. Current class labeling approved for other hormonal contraceptives will also be considered in reviewing sections such as Contraindications, Warnings and Precautions, Patient Counseling Information, etc..

It is premature to comment on the completeness of labeling at this time; labeling recommendations will be made during the review cycle.

Question 3

Medicines360 proposes that the requirements under the Pediatric Research Equity Act (PREA) are not applicable to the LNG20 IUS because it does not contain a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration. The product contains the same active ingredient (levonorgestrel) contained in numerous approved contraceptive products, including other IUS products (Mirena and Skyla). The strength (52 mg levonorgestrel) and release rate (approximately 20 µg/day) have also been approved in an IUS product.

If the Division determines that PREA is applicable, Medicines360 plans to satisfy the requirements under PREA as follows:

- a. Medicines360 plans to submit a partial waiver for females less than (b) (4) years of age and (b) (4) pre-menarcheal females are not at risk of pregnancy.*
- b. Medicines360 requests that the requirements for post-menarcheal pediatric patients be deemed fulfilled by extrapolation of data from females (b) (4) years of age and older.*
 - 3a. Does the Division agree that PREA does not apply to this product and that all post-menarcheal females may be included in the labeling?*
 - 3b. If PREA does apply, does the Division agree that the information provided in this meeting information package will be sufficient to satisfy the requirements for a pediatric assessment to be submitted with the NDA and to include all post-menarcheal females in the labeling?*

FDA Response:

Upon initial consideration, it appears that PREA does not apply to this product. However, the final determination will be made during the review cycle.

If the Sponsor opts to request a partial waiver and extrapolation from adult data, the age at which risk of pregnancy is not applicable is generally considered to be 0-11 years; it would be appropriate to seek a waiver of pediatric studies in girls within this age range. The Sponsor may propose extrapolation of efficacy data from adult women to adolescents from ages 12 to 15, inclusive.

Question 4

Medicines360 has obtained agreement with the Division as documented in the Type C meeting held 26 June 2012 (see Appendix 3) that the safety data for a menorrhagia study using LNG IUS (labeled as (b) (4)) conducted by Actavis would not be integrated into the Medicines360 Integrated Summary of Safety (ISS) but will be presented in Module 5 as a separate clinical study report. Medicines360 intends to submit this study as legacy information and plans to provide only the Clinical Study Report without the raw data in CDISC format.

Does the Division agree that this study can be submitted in Module 5 as a single PDF without the raw data?

FDA Response:

No. If possible, the data should be submitted to allow for analysis of safety information. Narratives should be submitted for the same adverse events (and pregnancies) as will be done for Study M360-L102.

The Division also requests that the submission discuss any significant inquiries about safety or efficacy that arose during the Medicines and Healthcare Products Regulatory Agency (MHRA) review of Levosert.

Question 5

A table listing key agreements reached between Medicines360 and the Division throughout the development program are summarized and provided in this meeting information package (Section 6.2.5).

- 5a. Does the Division agree that based on this information, the submission would be considered reviewable?*
- 5b. Medicines360 does not plan to do a database integration as agreed in the Type C meeting held 26 June 2012 (see Appendix 3) and will not have an ISE and/or ISS placed in Module 5 since only one Phase 3 study is being conducted and all efficacy and safety information from any of the Medicines 360 conducted studies will be presented and summarized in the appropriate Module 2 section (e.g., 2.7.1, 2.7.3, 2.7.4). Does the Division agree with this approach?*

FDA Response:

Upon preliminary consideration, it appears that the data to be submitted will allow for review of the application. The Division agrees with the Summary of Key Agreements presented in Table 12 with one exception: because the inserter proposed for use with the to-be-marketed product was not one of the two evaluated in the phase 3 study, careful consideration will be given to

information about the to-be-marketed inserter and to the data from the subset of subjects who experienced the THI-001 inserter. The Division requests that safety and efficacy data be presented separately for the two inserter subgroups to allow for evaluation of whether the different inserters appear to impact safety or efficacy. A pooled analysis should also be provided. The specific (sub)population used for the efficacy analysis to support labeling will be a review issue. See additional comments about the change in inserter in response to Questions 10 and 16.

The Division agrees that Integrated Summaries of Safety and Efficacy (ISS and ISE) are not required because a single phase 3 safety and efficacy study was conducted.

Question 6

Medicines360 is developing LNG20 IUS to provide low-cost, reliable, reversible contraception to low-income women in the US. Medicines360 plans to make its IUS available to uninsured and underinsured women in the US public sector at a price of (b) (4), compared to the approximately (b) (4) cost of Mirena. By providing an affordable contraceptive option to women in this socioeconomic demographic, Medicines360 will provide greater access to women who need IUSs and thereby begin to ameliorate the epidemic of unplanned and potentially unwanted pregnancies in this population, and the associated negative health outcomes such as repeat abortions.

Because LNG20 IUS is expected to fill a critical unmet medical need, does the Division agree that the LNG20 IUS NDA would be eligible for priority review?

FDA Response:

The Division is unable to take pricing information in consideration in determining whether a product addresses an unmet need. As discussed in the June 2012 meeting, the application does not appear to meet the criteria for priority review, but this determination will be made after the NDA is submitted.

Question 7

The NDA will be submitted as an electronic submission. The submission will be XML formatted with eCTD Manager, purchased from (b) (4) software will be utilized to ensure that the submission is virus-free. The submission will be made on behalf of Medicines360 by (b) (4), who have been appropriately trained by (b) (4), in the use of their e-submission software.

Does the Division find the proposal for eCTD submission acceptable?

FDA Response:

Yes.

Question 8

The electronic NDA submission will include all tables and listings from the pivotal Phase 3 study (M360-L102) generated for the clinical study report (samples provided in the meeting information package), and analysis data sets conforming to CDISC submission standards. Case report forms and narratives for serious adverse events (SAEs), deaths, pregnancies, and discontinuation due to adverse events (AEs) will also be provided. ADaM data set structures will include information pertaining to the number of 28-day cycles of exposure for direct calculation

of the Pearl Index. SAS programs that generate all tables and listings will be provided, as requested by Division review staff.

Does the Division find Medicines360's proposal for submission of efficacy and safety data acceptable?

FDA Response:

Yes; however, the Division also requests that a cumulative Pearl Index through three years of treatment be presented (see response to Question 11).

The Division also requests that the Sponsor address IUS-specific safety concerns including perforations, expulsions (partial and total), pelvic infections (uterine [endometritis] and more generalized [Pelvic Inflammatory Disease]), ectopic pregnancies, ovarian cysts, dysmenorrhea, etc. Data pertaining to insertion and removal (failed insertions and removals, broken strings, and reasons for removal, as well as data on ease/pain of insertion and removal from the healthcare provider and patient perspective, respectively, if obtained) is needed and should be stratified by inserter used. Data on return to fertility after discontinuation of the IUS should be presented as available (i.e., in women who discontinued with the intent of conceiving).

Clinical

Question 9

The Phase 3 study (M360-L102) achieved its enrollment target of 1910 subjects on 23 April 2013. The study is ongoing. Medicines360 achieved a minimum of 200 subjects who completed 3 years of use in July 2013. Medicines360 performed a data cut on 12 July 2013 for the purpose of creating a locked database for an NDA submission planned for December 2013. The characteristics of the 12 July 2013 dataset are described in 6.3.1.

Does the Division agree that this dataset described in this section is adequate for NDA filing to support a 3-year label indication?

FDA Response:

It appears that the dataset will be adequate to support an application for a three-year indication; however, the final determination will be made during the review cycle.

Question 10

Medicines360 intends to evaluate the efficacy and safety results of its Phase 3 clinical study (M360-L102) per the specifications of the revised Statistical Analysis Plan (SAP), version 2.0, dated 20 February 2013 and submitted to the Division on 22 February 2013 (SN0049). In SN0049, Medicines360 addressed the Division's recommendations that appeared in its letter dated 13 December 2012.

Does the Division agree that the proposed evaluations of efficacy and safety as elucidated in the revised SAP (SN0049) are acceptable for the NDA submission?

FDA Response:

The inclusion of secondary efficacy analyses in older women and subgroups based on age, ethnicity, parity and BMI is acceptable. The Division will evaluate the efficacy data in subgroups based upon inserter-type. Should a marked discrepancy in effectiveness be apparent,

further exploration may be needed, including presentation of Pearl Indices and 95% confidence limits for each subgroup.

Question 11

Medicines360 plans to seek a 3-year use indication in its marketing application for LNG20 IUS. At the time of NDA filing, the dataset from the 12 July 2013 data cut is expected to exceed the minimum requirements discussed in the Type C meeting held 26 June 2012 (see Appendix 3). Efficacy will be evaluated as follows:

- a. The primary efficacy endpoint is the Pearl Index in subjects 16 – 35 years of age, inclusive, based on (b) (4) ear data from the July 2013 data cut as described in the SAP, version 2.0.*
- b. Pearl Indices in subjects 16 – 35 years of age, inclusive, will also be calculated for the 1-year and 3-year data from the July 2013 data cut as described in the SAP, version 2.0.*
- c. Acceptable precision for the Pearl Index (defined as the upper bound of the 95% CI being no more than 1 unit greater than the point estimate) will be reached for subjects 16 – 35 years of age, inclusive.*
- d. An acceptable Pearl Index will be demonstrated for subjects 16 – 35 years of age, inclusive.*

Does the Division agree with this approach for evaluating efficacy to support a 3-year labeling indication?

FDA Response:

The Division does not agree that the single primary efficacy consideration is the two-year Pearl Index. The acceptability of the Year 1, Year 2, Year 3 and cumulative three-year Pearl Indices will all be considered in evaluating efficacy. Failure to demonstrate an acceptable Pearl Index at any of these intervals would be a significant review issue.

Question 12

In the Pre-IND Meeting Minutes (issued 09 October 2009; Appendix 2) the Division stated that

*(b) (4)
The number and percentage of nulliparous LNG20 subjects enrolled in the Phase 3 study are provided in Section 6.3.4.*

(b) (4)

FDA Response:

(b) (4)

Question 13

The data cutoff for the database lock for the 120-day safety update will be set at 3 months prior to the due date based on the NDA submission date. This data cutoff date in this ongoing study

represents 6 additional months from the data cutoff date (i.e., July 2013) that is set for the NDA submission.

Does the Division agree that the proposed lead time for the data cutoff date is acceptable?

FDA Response:

Yes.

Question 14

*Medicines360 is providing in this meeting information package preliminary efficacy data representative of the final cleaned database of 12 July 2013 provided for the NDA (Section **Error! Reference source not found.**).*

The efficacy profile submitted with the NDA is expected to be similar to that presented in this meeting information package. Does the Division anticipate that these data would be adequate to support filing and sufficient to allow review of efficacy of the product?

FDA Response:

Yes. However, the Sponsor should discuss the impact on efficacy of missing data about the use of other birth control methods if there is extensive missing data. Clarify how data on use of back-up contraception was ascertained in each of the three years of the trial.

Question 15

Medicines360 is providing in this meeting information package preliminary safety data representative of the final cleaned database of 12 July 2013 provided for the NDA (Section 6.3.6.3).

The safety profile submitted with the NDA is expected to be similar to that presented in this meeting information package. Does the Division anticipate that these data would be adequate to support filing and sufficient to allow review of safety of the product?

FDA Response:

Yes. Clarify how bleeding data was ascertained in each of the three years of the trial (i.e., was a daily diary used for all three years?).

Question 16

Medicines360 intends to market the LNG20-IUS with an optimized 2-handed inserter. An earlier version of this 2-handed inserter was used in the first 760 subjects enrolled in the Phase 3 clinical study. This inserter was subsequently optimized as described below.

Medicines360 considers the changes made in the optimization to be minor changes. As such, Medicines360 proposes that the data generated during the Phase 3 clinical study provides sufficient insertion-related data on the LNG20 IUS for FDA's review and approval of the to-be-marketed product. Does the Division agree?

FDA Response:

No, FDA does not agree. Ideally, the final finished combination product should be studied in phase 3. The extent to which this to-be-marketed inserter (THI-002) is supported by data obtained from use of the THI-001 inserter in the phase 3 trial will be determined during the NDA review.

From a clinical perspective, the Sponsor should clarify whether the Levosert menorrhagia trial utilized the THI-002 inserter. Also clarify whether Study M360-L103 obtained any data based on the THI-002 inserter. [REDACTED] (b) (4)

The Center for Devices and Radiologic Health (CDRH) will be involved in the review of the to-be-marketed inserter and the extent to which the Sponsor has characterized the potential impact of the modified inserter on the performance of the IUS. Currently, the specifics of the changes from the THI-001 to the -002 inserter are poorly characterized in the meeting package.

In order to assist in the review, the following is an example of the type of information to submit in the NDA

- a) An exposure and safety profile stratified by the two inserters used in the clinical trial. This should include, but is not limited to, product quality defects, medical device failures and any associated subject events as well as delayed events such as expulsion and perforation.
- b) [REDACTED] (b) (4)
- c). Detailed description, characteristics, and performance validation of the THI-002 inserter
- d). Detailed design differences between the THI-001 and the THI-002 inserter
- e). Detailed performance characteristics of the THI-002 inserter as they relate to the IUS
- f). Detailed information on the Hazard Risk Analysis and basis for design changes to mitigate risks associated with the THI-002 inserter and how the changes were validated. [REDACTED] (b) (4)
- g). Justify why a design change from the THI-001 inserter to the THI-002 inserter will not result in meaningful changes in PK parameters of levonorgestrel.

FDA may provide additional comments in the final meeting minutes or in a subsequent communication.

In addition, regarding manufacturing practice for combination products, the Sponsor is reminded that combination products are subject to 21 CFR Part 4 – Current Good Manufacturing Practice Requirements for Combination Products accessible at

<https://www.federalregister.gov/articles/2013/01/22/2013-01068/current-good-manufacturing-practice-requirements-for-combination-products>.

Ex Vivo Release

Question 17

Reference is made to the Type C meeting held 26 June 2012 (see Appendix 3) in which the Division agreed that the in vivo release rate could be calculated by measuring the residual content of levonorgestrel based on sampling of IUS units that have been expelled or removed. Medicines360 proposes sampling and testing of N = 6 LNG20 IUS units per 90-day interval through the first 2.5 years and N = 6 per 180-day interval thereafter (or the remaining 0.5 years [180 days] of the of 3-year study duration).

A statistical analysis of IUS residual content samples (N = 52) over the first (b) (4) years as proposed above demonstrated that the sample plan is sufficiently powered (95%) to characterize the in vivo release rate.

Does the Division agree that this sampling and analysis plan is adequate to evaluate the in vivo release rate?

FDA Response:

The Sponsor's proposed plan and data appear to be reasonable to evaluate the *in vivo* release rate. However, the determination on the adequacy of the data to evaluate the *in vivo* release rate will be made at the time of NDA review.

Nonclinical

Question 18

At the Pre-IND Meeting held in September 2009 (minutes issued 09 October 2009, response to Question 4; Appendix 2), the Division agreed that Medicines360 could rely on nonclinical information from the public domain to satisfy the nonclinical requirements for levonorgestrel and the implanted device and that no additional nonclinical studies were necessary at this time. Medicines360 intends to rely on the following information to satisfy the nonclinical requirements for the LNG20 IUS NDA:

- a. Information on levonorgestrel from the public domain:*
 - 1. The nonclinical toxicology information (repeat-dose toxicity, carcinogenesis, mutagenesis, and reproductive toxicity) from published studies in the literature*
 - 2. Nonclinical data from the published literature that evaluates the safety of intrauterine use of levonorgestrel-containing polydimethylsiloxane delivery systems*
- b. Nonclinical biocompatibility studies on the components of the delivery system conducted by Medicines360 or to which it has right of reference:*
 - 1. 90-day toxicology study (subdermal implant) conducted to evaluate the safety of the drug reservoir and membrane (Study In 020/07-0189)*
 - 2. Biocompatibility studies conducted to evaluate the safety of the thread, drug reservoir, membrane, T-frame, and inserter*

This information is expected to fulfill all nonclinical regulatory requirements for product approval; therefore Medicines360 does not plan to rely upon a listed drug in its 505(b)(2) NDA. Please note that this represents a different approach than discussed in the Pre-IND Meeting Minutes (issued 09 October 2009; Appendix 2), (b) (4)

Does the Division agree that reliance on these data, which will be provided in the LNG20 IUS NDA (summarized in this section), is appropriate and that no additional nonclinical safety data will be required for NDA submission?

FDA Response:

Yes, the Division agrees, pending review of the submission, and does not anticipate requiring any additional nonclinical studies at this time. The Sponsor is reminded that reliance on published literature describing a listed drug(s) is considered to be reliance on FDA's finding of safety and/or effectiveness for the listed drug(s) (see response to Question 1).

Chemistry, Manufacturing, and Controls

Please note, as a follow-up to feedback received at the Type C meeting held 26 June 2012 (see Appendix 3), Medicines360 is providing the following clarification. Medicines360 has revised the drug product manufacturing plan for the NDA and now proposes to manufacture drug product at the same manufacturing site used for Phase 3 clinical drug product and primary (registration) stability batches.

Drug Product

Question 19

Does the Division agree that the proposed drug product stability data package is adequate to support acceptance of the NDA for filing?

FDA Response:

The proposed stability data package, which includes up to 48 months of data on 3 primary stability lots, 18 months of data on one lot, and 6 months on three additional lots appears adequate to support acceptance of the NDA for filing.

Question 20

Does the Division agree that the proposed drug product specifications are adequate to support acceptance of the NDA for filing?

FDA Response:

The proposed drug product specifications appear adequate to support the NDA filing. The Sponsor is reminded that the adequacy of the acceptance criteria is an NDA review issue. For the impurities, please list the identified impurities by name and not a code number.

FDA cannot comment on the adequacy of the proposed *in vitro* release specifications without reviewing the data. The *in vitro* release specifications should be supported by sufficient data and appropriate justification including the selection of the time points and the acceptance criteria. Provide supportive data/information to justify the proposed *in vitro* release specifications in the NDA.

A consult has been sent to CDRH for advice on any additional information they will need for review of the inserter, including information needed to determine if a device-specific inspection would be needed. This is discussed, in part, in the response to Question 16.

Question 21

Regarding the drug product release method:

Does the Division agree with Medicines360 that information generated from either the completed studies or the planned studies is sufficient to support the adequacy of the proposed drug release method?

FDA Response:

The proposed outline of the *in vitro* release report seems reasonable, although the adequacy of the method will be determined after the report is reviewed. The following comments should be noted:

- As requested during the meeting held June 26, 2012, the *in vitro* release data should be reported as the cumulative drug release with time and the release profile should be complete and cover at least (b) (4) % of drug release of the label amount or whenever a plateau (b) (4) is reached.
- Based on FDA's experience, the agitation speed (b) (4) seems high. Test more agitation speeds (b) (4)
- Provide the complete *in vitro* release profile data (individual, mean, SD, profiles) of all batches available for the product.

Question 22

Are there any other studies or information that the Division recommends to include in the method development report?

FDA Response:

On page 95 of the meeting package, the Sponsor stated that the NDA will include data from three batches. Please include the data from all batches available.

Additional comments:

The *in vitro* drug release profiles presented in Figure 6 on page 89 should be reported as the cumulative drug release with time and then compared using the f2 matrix to support the similarity between the products before and after the changes.

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of the criteria apply at this time to your application, you are exempt from these requirements. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

PRESCRIBING INFORMATION

In its application, the Sponsor must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. As the Sponsor develops its proposed PI, the Division encourages the Sponsor to review the following labeling review resources: the Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products, labeling guidances, and a sample tool illustrating the format for Highlights and Contents (Table of Contents) available at: <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm>.

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your 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.				

DEVICE MANUFACTURING PROCESS:

- a) All device constituent-associated documents should be located in Section 3.2.P.7 - Container Closure System. These should include information pertaining to manufacturing or assembly of the finished combination product and documents necessary to demonstrate compliance with applicable 21 CFR part 820 regulations.
- b) The list of manufacturing facilities provided on the Form FDA 356h, or as an attachment to the form, should explicitly describe the manufacturing, assembly, or testing processes taking place at each site with regards to the device constituent part.
- c) Suggestions on the types of documents to submit for review can be found in the guidance document titled “Quality System Information for Certain Premarket Application Reviews; Guidance for Industry and FDA Staff,” issued on February 3, 2003. The complete document may be found at <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070897.htm>
- d) To facilitate the review process, include an Application Roadmap, identifying documents addressing 21 CFR part 820 regulations, and the manufacturing of the finished combination product.

505(b)(2) REGULATORY PATHWAY

A 505(b)(2) application would be an acceptable approach at this time based on the information provided. The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency’s regulations at 21 CFR 314.54, and the draft guidance for industry *Applications Covered by Section 505(b)(2)* (October 1999), available at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions that had challenged the Agency’s interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at <http://www.regulations.gov>).

If the Sponsor intends to submit a 505(b)(2) application that relies for approval on FDA’s finding of safety and/or effectiveness for one or more listed drugs, it must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). The Sponsor should establish a “bridge” (e.g., via comparative bioavailability data) between its proposed drug product and each listed drug upon which it proposes to rely to demonstrate that such reliance is scientifically justified.

If the Sponsor intends to rely on literature or other studies for which it has no right of reference but that are necessary for approval, it also must establish that reliance on the studies described in the literature or on the other studies is scientifically appropriate. The Sponsor should include a copy of such published literature in the 505(b)(2) application and identify any listed drug(s) described in the published literature (e.g., trade name(s)).

If the Sponsor intends to rely on the Agency’s finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s) (which is considered to be reliance on FDA’s finding of safety and/or effectiveness for the listed drug(s)), it should identify the listed drug(s) in accordance with the Agency’s regulations at 21 CFR 314.54. It should be noted that 21 CFR 314.54 requires identification of the “listed drug for which FDA has made a finding of safety and effectiveness,” and thus an applicant may only rely upon a listed drug that was approved in an NDA under section 505(c) of the FD&C Act. The regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

If the Sponsor proposes to rely on FDA’s finding of safety and/or effectiveness for a listed drug that has been discontinued from marketing, the acceptability of this approach will be contingent on FDA’s consideration of whether the drug was discontinued for reasons of safety or effectiveness.

The Sponsor is encouraged to identify each section of its proposed 505(b)(2) application that relies on FDA’s finding of safety and/or effectiveness for a listed drug(s) or on published literature. In the 505(b)(2) application, the Sponsor is encouraged to identify clearly (for each section of the application, including the labeling): (1) the information for the proposed drug product that is provided by reliance on FDA’s finding of safety and/or effectiveness for the listed drug or by reliance on published literature; (2) the “bridge” that supports the scientific appropriateness of such reliance; and (3) the specific name (e.g., proprietary name) of each listed drug named in any published literature on which the marketing application relies for approval. If the Sponsor is proposing to rely on published literature, include copies of the article(s) in the submission.

In addition to identifying in the annotated labeling the source(s) of information essential to the approval of the proposed drug that is provided by reliance on FDA’s previous finding of safety and efficacy for a listed drug or by reliance on published literature, the Division encourages the Sponsor also to include that information in the cover letter for its marketing application in a table similar to the one below.

List the information essential to the approval of the proposed drug that is provided by reliance on the FDA’s previous finding of safety and efficacy for a listed drug or by reliance on published literature	
Source of information (e.g., published literature, name of listed drug)	Information Provided (e.g., specific sections of the 505(b)(2) application or labeling)
<i>1. Example: Published literature</i>	<i>Nonclinical toxicology</i>
<i>2. Example: NDA XXXXXX “TRADENAME”</i>	<i>Previous finding of effectiveness for indication X</i>
<i>3. Example: NDA YYYYYY “TRADENAME”</i>	<i>Previous finding of safety for Carcinogenicity, labeling section XXX</i>

Please be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were approved before the Sponsor's application is submitted, such that its proposed product would be a "duplicate" of a listed drug and eligible for approval under section 505(j) of the FD&C Act, then it is FDA's policy to refuse to file the application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the appropriate submission would be an Abbreviated New Drug Application (ANDA) that cites the duplicate product as the reference listed drug.

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 those inspections (Item I and II). This information is requested for all major trials used to support safety and efficacy in the application (i.e. phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to 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 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

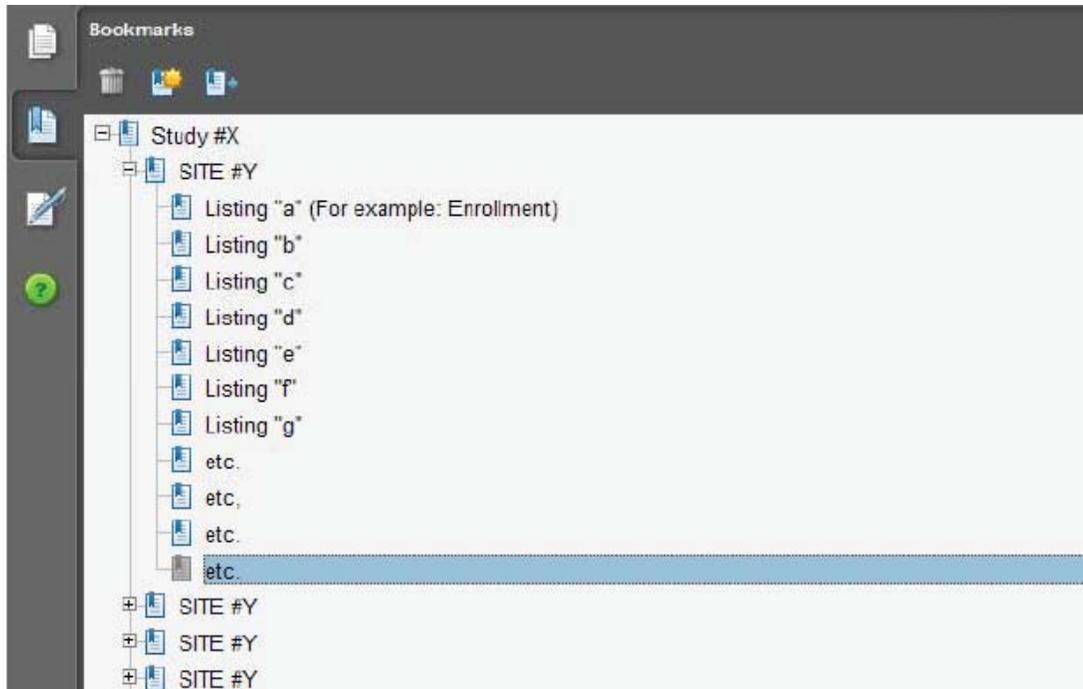
I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal 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. Location of Principal Investigator: Address (e.g. Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.
2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
 - a. Number of subjects screened at each site
 - b. Number of subjects randomized at each 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 pivotal clinical trials:
 - a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection

- b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g. as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
 - c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.
4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
 5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as “line listings”). For each site, provide line listings for:
 - a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
 - b. Subject listing for treatment assignment (randomization)
 - c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
 - d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
 - 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, including a 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 testing (e.g., laboratory, ECG) 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. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft “Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER’s Inspection Planning” (available at the following link <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf>) for the structure and format of this data set.

Attachment 1

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/BLA 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/

ZETA-MAE C WILLIAMSON
09/13/2013