

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

206229Orig1s000

CHEMISTRY REVIEW(S)

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: February 26, 2015
FROM: Nina Ni, Ph. D., Review Chemist, Branch II, DNDP I/ONDP
THROUGH: Moo-Jhong Rhee, Ph. D., Branch Chief, Branch V, DNDP II/ONDP
TO: NDA 206229
SUBJECT: Addendum to CMC Review #1 and Addendum #1 for NDA 206229

Nina Ni -S
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DN: c=US, o=U.S. Government, ou=HHS,
ou=FDA, ou=People on Move to S,
ou=2342.10200300.100.1.1, 2015022605
Date: 2015.02.26 10:15:58 -05'00'

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In my Addendum #1, dated 02/11/2014, this NDA was recommended for approval from a CMC perspective. However, recently the applicant has updated below labeling by defining the role of Medicines360 and found adequate.

- **Carton and Container Labels**

Carton Label:

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MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: February 11, 2015
FROM: Nina Ni, Ph. D., Review Chemist, Branch II, DNDP I/ONDP
THROUGH: Moo-Jhong Rhee, Ph. D., Branch Chief, Branch V, DNDP II/ONDP
TO: NDA 206229
SUBJECT: Final recommendation for NDA 206229

Nina Ni
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DN: cn=US, o=US Government
ou=HHS, ou=FDA, ou=People
center, cn=Ni, S
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00192000
Date: 2015 02 11 07 57 48
05 00

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ou=FDA, ou=People, cn=Moojhong Rhee
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Date: 2015 02 11 09:25:04 05'00

In my CMC Review #1, dated 12/19/2014, this NDA was recommended for not approval due to the following issues:

1. Specification of the drug product has not been satisfactorily established due to pending recommendations for sterility (Micro Review) and drug release rate (Biopharm Review). Also the functionality of the inserter has not been satisfactorily determined (CDRH Review).
2. The Office of Compliance has not made an overall “Acceptable” recommendation for the manufacturing facilities.
3. Label/labeling issues were not satisfactorily resolved yet.

As of the date of this memorandum, the specification of the drug product has been satisfactorily established for sterility (see Micro review, dated 01/23/2015), drug release rate (see Biopharm review, dated 01/16/2015), and functionality of the inserter (see CDRH review, dated 01/26/2015).

The Office of Compliance has also issued an overall “Acceptable” recommendation (date: 02/02/2015 see the **Attachment 1**).

The following deficiencies pertinent to the labeling have been satisfactorily updated as described below (see the **Attachment 2**):

“How Supplied” Section

- Manufacturer/distributor name was added.

Carton Labels

- The statement of “see package insert for dosage information” was added.

Recommendation:

All previous unresolved issues have been satisfactorily resolved. Therefore, from the ONDP perspective, this NDA is recommended for approval.

Attachments:

Attachment 1: Recommendation from Office of Compliance:

NDA 206229-Orig1-New/NDA(1)

Page 1 of 3

Because you're using an older browser, your ATask experience isn't all that it should be. We seriously recommend [exploring other options](#).

NDA 206229-Orig1-New/NDA(1)

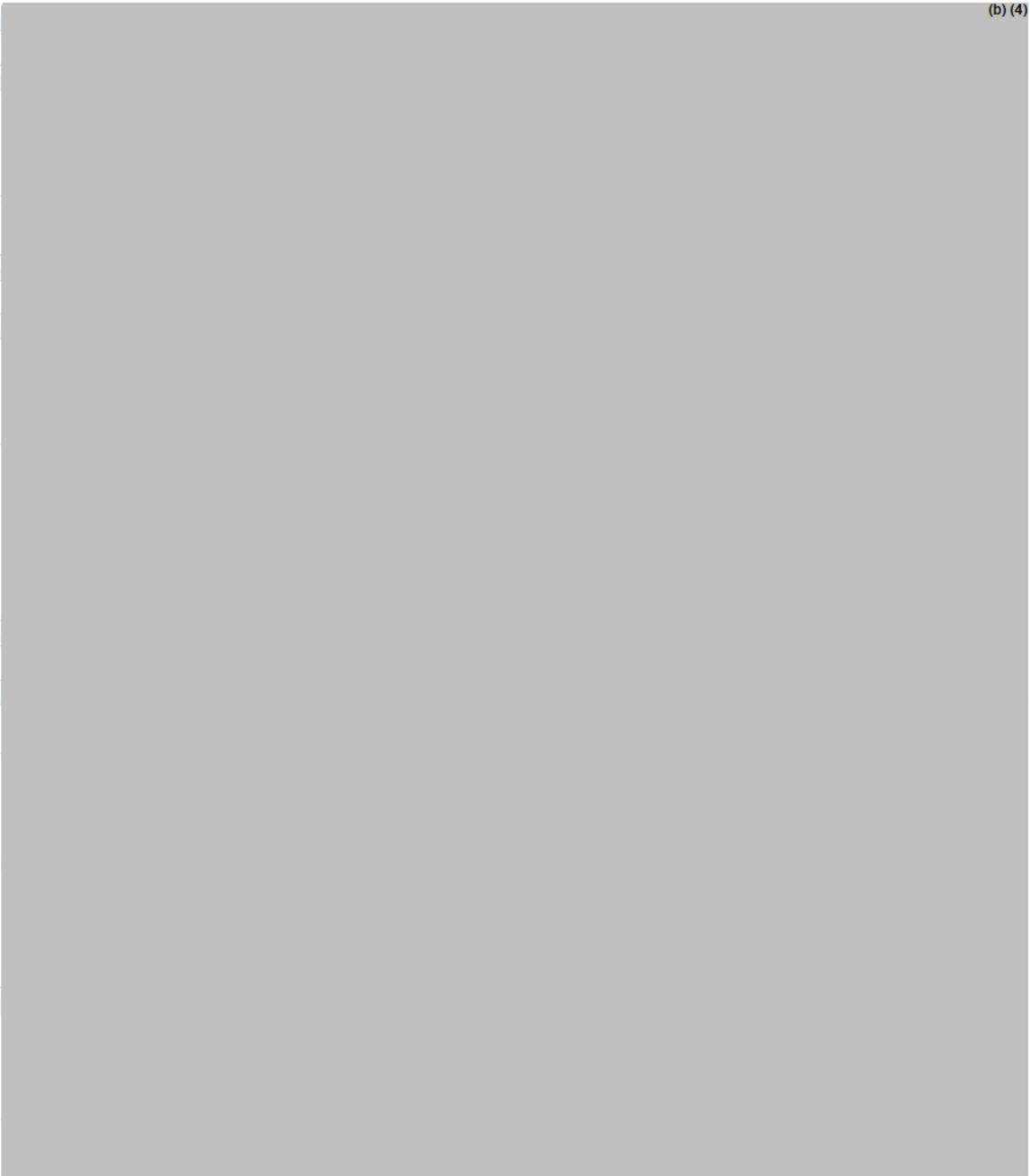
Edit Export More

#	Task Name	Task Instructions	Assigned To	Pln Comp	Act Comp	Task Status	Task Actions
Parent: Manufacturing Facility Inspection (3)							
86	Application Specific Inspection Criteria	If you are finished with this task, change the Task Status to Complete.		7/13/14	10/8/14	Complete	
87	Assign Profile Code Selection Tasks			5/29/14	10/8/14	Complete	
164	Overall Manufacturing Inspection Recommendation		Vpuchandra Dholakia	7/13/14	1/30/15	Complete	

(b) (4)



(b) (4)



Parent: Facility: ODYSSEA PHARMA FEI: 3007966308 (1)						
<input type="checkbox"/>	149	Enter Profile Codes	5/30/14	11/6/14	Complete	
Parent: Profile Evaluation for ODYSSEA PHARMA - NEC NOT ELSEWHERE CLASSIFIED FEI: 3007966308 (6)						
<input type="checkbox"/>	151	Enter Facility Specific Criteria NEC NOT ELSEWHERE CLASSIFIED	DARRTS Migration	5/30/14	11/6/14	Complete
<input type="checkbox"/>	152	Office of Process and Facilities Decision/Request NEC NOT ELSEWHERE CLASSIFIED		5/31/14	11/6/14	Complete

<input type="checkbox"/> 153	District Office Decision/Request NEC NOT ELSEWHERE CLASSIFIED	Meredith Rose	6/1/14	11/6/14	Complete
<input type="checkbox"/> 154	Inspect Facility and Receive FACTS Results		6/2/14	1/14/15	Complete
<input type="checkbox"/> 155	District Office Recommendation NEC NOT ELSEWHERE CLASSIFIED	Elizabeth Philpy	6/3/14	1/30/15	Complete
<input type="checkbox"/> 156	Office of Process and Facilities Recommendation NEC NOT ELSEWHERE CLASSIFIED	Vipuchandra Dholakia	6/4/14	1/30/15	Complete

(b) (4)

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS)
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NDA 206229

**Liletta[®] (levonorgestrel-releasing intrauterine system)
52 mg**

Medicines360

Nina Ni, Ph. D.

Review Chemist

Branch IV

**Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment**

CMC REVIEW

For the Division of Reproductive & Urology

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CMC Review Data Sheet

CMC Review Data Sheet

1. NDA 206229
2. REVIEW #: 1
3. REVIEW DATE: 12/19/2015
4. REVIEWER: Nina Ni, Ph. D.
5. PREVIOUS DOCUMENTS:
6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original Submission	04/30/2014
Correspondence (C)	
Amendment (BC): 0001	05/19/2014
Amendment (BC): 0006 reviewed by Dr. Miller	07/31/2014
Amendment (BC): 0010	11/20/2014
Amendment (BC): 0011 reviewed by Dr. Price	11/26/2014

7. NAME & ADDRESS OF APPLICANT:

Name: Medicines360
Address: 353 Sacramento St. Suite 900
San Francisco, CA 94111
Representative: Andrea Olariu, M. D., Ph. D.
Telephone: 415-403-8925
Email: aolariu@medicines360.org

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Liletta[®] (proposed)
- b) Non-Proprietary Name (USAN): Levonorgestrel
- c) Code Name/# (ONDQA only): LNG20, LNG
- d) Chem. Type/Submission Priority (ONDQA only):
 - Chem. Type: 5
 - Submission Priority: Standard

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

CMC Review Data Sheet

10. PHARMACOL. CATEGORY: For prevention of pregnancy for up to 3 years

(b) (4)

11. DOSAGE FORM: Intrauterine contraceptive system (IUS)

12. STRENGTH/POTENCY: 52 mg/IUS, 18.6 µg/day

13. ROUTE OF ADMINISTRATION: Intrauterine

14. Rx/OTC DISPENSED: Rx OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

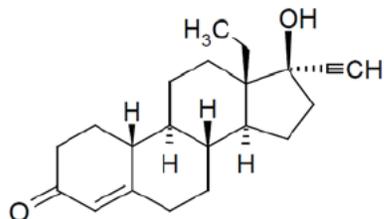
Not a SPOTS product

1. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

NAME: Levonorgestrel

CHEMICAL NAME: 18,19-dinorpregn-4-en-20-yn-3-one,13-ethyl-17-hydroxy-,(17 α)-(-)-; (-)-13-ethyl-17-hydroxy-18,19-dinor-17 α -pregn-4-en-20-yn-3-one; (17 α)-(-)-13-ethyl-17-hydroxy-18,19,dinorpregna-4-en-20-yn-3-one

STRUCTURAL FORMULA:



MOLECULAR FORMULA: C₂₁H₂₈O₂

MOLECULAR WEIGHT: 312.45

CAS NUMBER: [797-63-7]

CMC Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	Drug Substance	3	Adequate	03/12/2014	By X. Zhang
	IV		(b) (4)	1	Adequate	11/25/2014	By N. Ni
	IV			1	Adequate	11/25/2014	By N. Ni
	III			4	N/A		
	III				pending		Reviewed by CDRH

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 –Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	105836	
NDA		

CMC Review Data Sheet

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	NA		
EES	Pending		
Pharm/Tox	NA		
Biopharm	Pending		Kelly Kitchens, Ph. D.
LNC	NA		
Methods Validation	NA, according to the current ONDQA policy.		
DMEPA	NA		
EA	Claim for the categorical exclusion is granted. See IQA	05/30/2014	R. Bloom, Ph. D.
Microbiology	Pending		Denise Miller, Ph. D.
CDRH	Pending		Veronica Price, Ph. D.

The CMC Review for NDA 206229

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The applicant has *not* provided sufficient information to assure the identity, strength, purity, and quality of the drug product.

The Office of Compliance has *not* made an overall “Acceptable” recommendation for the facilities involved in this NDA.

Also, issues on label/labeling have *not* been resolved.

Therefore, from the ONDQA perspective, this NDA is *not* ready for approval in its present form until all the pending issues are satisfactorily resolved.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

NA

II. Summary of CMC Assessments

The microbial control information for the drug substance, excipients, and drug product is reviewed by microbiologist, Denise Miller, Ph. D.

The drug release profile of the drug product at release and during stability study is reviewed by Kelly Kitchens, Ph.D.

The inserter and removal thread are considered device components and reviewed by CDRH.

The following assessments do not include the aforementioned attributes due to pending their recommendations.

Description of the Drug Product(s) and Drug Substance(s)

(1) Drug Substance

The drug substance proposed under this NDA is levonorgestrel, USP (b) (4), which is a well characterized synthetic progestin and has been widely used in different approved hormonal contraceptive products, including intrauterine devices. All

CMC Assessment Section

information related to the manufacturing and controls are referenced to (b) (4) Drug Master File (DMF) (b) (4). This DMF was previously found adequate to support the ANDA 201088 (tablets, 2013) as well as (b) (4). No changes are reported to the DMF since the last review. Based on this, DMF (b) (4) is considered adequate to support this NDA. In addition to DMF (b) (4), the applicant has provided satisfactory batch data for drug substances used in the manufacturing of clinical and stability batches of drug product.

(2) Drug Product

The proposed drug product is a levonorgestrel (LNG)-releasing intrauterine system (IUS), which consists of a T-shaped polyethylene frame (T-frame) with a (b) (4) reservoir (drug reservoir) around the vertical stem.

The drug reservoir consists of a cylinder made of a mixture of LNG and polydimethylsiloxane (PDMS) formed from silicone base, tetra-n-propyl silicate, and stannous octoate. (b) (4)

Each LNG drug reservoir (b) (4) contains 52 mg of USP grade (b) (4) LNG.

The drug reservoir is covered with a PDMS membrane. The T-frame has an eyelet at one end of the vertical stem and two horizontal arms at the other end. The low-density polyethylene of the T-frame is compounded with barium sulfate, which makes it radio opaque. A blue polypropylene monofilament removal thread is attached to the eyelet at the end of the vertical stem of the T-frame.

Each drug product is placed within an inserter tube that is used for insertion into the uterus. The inserter tube consists of a (b) (4) that is printed with a graduated scale, and is supplied with a (b) (4) flange and (b) (4) pusher. The drug product and inserter tube will be packaged in a pouch constructed of (b) (4) and (b) (4) on one side, and (b) (4) on the other side.

The following non-compendial excipients have been used: silicone base, tetra-n-propyl silicate, stannous octoate, (b) (4) low density polyethylene (LDPE), barium sulfate, polydimethylsiloxane (PDMS) membrane, and polypropylene thread (b) (4) with (b) (4) copper. Adequate controls are in-place for each non-compendial excipient.

(b) (4)

Both DMFs are reviewed and found adequate to support this NDA. No safety concern is raised for these two novel excipients from Pharmacology Toxicology perspective as well, see Pharm Tox review dated 12/10/2014 for a detailed discussion.

CMC Assessment Section

The manufacturing process for the drug product consists of [REDACTED] (b) (4)

The specification includes appearance (visual inspection), identification (HPLC), assay (HPLC), content uniformity (HPLC), degradation products (HPLC), drug release, [REDACTED] (b) (4)

[REDACTED] The proposed specification deem adequate to assure the identity, strength, purity, and quality of the drug product unless there is any drug release, microbiology issues, or inserter functionality issues noted by Biopharm reviewer, Microbiology reviewer, or CDRH reviewer, respectively.

Stability data (accelerated and long term) are provided for three primary stability batches (size: [REDACTED] (b) (4)) and four supportive stability batches (size [REDACTED] (b) (4) for one Phase III clinical batch and [REDACTED] (b) (4) for the other three supportive stability batches) manufactured in the intended commercial manufacturing site. The stability data indicate that the drug product is physically and chemically stable with no significant change when stored at [REDACTED] (b) (4) for up to 48 months and at [REDACTED] (b) (4). All tested attributes are within the specification without significant trending. The stability data support the proposed expiration dating period of 48 months for LNG 20 IUS when stored at 20 to 25°C (68 to 77°F) in outer carton until use to protect from light, excursions permitted to 15 - 30°C (59 - 86°F).

There is no in-use stability data provided in the submission. Considering the nature of the proposed drug product, it will be used as intrauterus device and will stay in the uterus for 3 years, the applicant should provide in-use stability data. However, lack of in-use stability data deems acceptable based on the following risk assessments:

- LNG is very stable compound. The applicant has provided 48 months stability data at 25°C and 15 months stability data at 40°C. All data show there is no change for all tested attributes.
- There is very low extractable observed for the [REDACTED] (b) (4)
- There are two approved drug products, Mirena and Skyla, which were approved without in-use stability data. Both drug products have been in the market for a long time (Mirena was approved in December, 2000 and Skyla was approved in January, 2013). Both Mirena and Skyla are very similar to the proposed drug product in this NDA in terms of: drug substance, indication, dosage form, delivery route, and use period.
- Pharm Tox reviewer, Krishan Raheja, Ph. D., has been consulted and confirmed that there is no safety concern from a Pharm Tox perspective for lack of in-use stability data.

CMC Assessment Section

B. Description of How the Drug Product is Intended to be Used

Levonorgestrel (LNG)-releasing intrauterine system (IUS) is inserted into uterine cavity by a trained healthcare professional. IUS is used to prevent pregnancy for up to 3 years (b)(4). The IUS itself contains 52 mg of levonorgestrel (LNG) that is initially released at 18.6 µg/day. This rate decreases progressively to 12.6 µg/day (b)(4) 3 years.

C. Basis for Approvability or Not-Approval Recommendation

21 CFR 314.125 (b)(1)

- Specification of the drug product has not been satisfactorily established due to pending recommendations for sterility (Micro Review) and drug release rate (Biopharm Review). Also the functionality of the inserter has not been satisfactorily determined (CDRH Review).

21 CFR 314.125 (b)(13)

- The Office of Compliance has not made an overall “Acceptable” recommendation for the manufacturing facilities.

21 CFR 314.125 (b)(6)

- Issues on labels and labeling have not been resolved yet.

(see the **List of the Deficiencies** on p. 135).

III. Lifecycle Knowledge Management

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	Factors that can impact the CQA	Risk Ranking*	Risk Mitigation approach in control strategy	Risk Evaluation	Lifecycle Considerations/ Comments**
Assay	<ul style="list-style-type: none"> • Formulation • Raw materials • Process parameters • scale/equipment • Site 	L	LNG was added to the formulation at (b)(4)% of the total weight to ensure an adequate supply of LNG in the	Acceptable	

CMC Assessment Section

			drug (b) (4) for long term use		
Physical stability (solid state)	(b) (4)	L	Particle size is controlled for drug substance	Acceptable	
Content Uniformity		L		Acceptable	
IVRT		L		Acceptable	
Leachables		M	(b) (4)	Acceptable	
Impurities/related substances/residual solvents		L	Drug product is very stable	Acceptable	
Sterility		M		Acceptable	

*Risk ranking applies to product attribute/CQA

**For example, post marketing commitment, knowledge management post approval, etc.

CMC Assessment Section

IV. Administrative

A. Reviewer's Signature:

(See appended electronic signature page) Nina Ni -S

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ou=FDA, ou=People, cn=Nina Ni -S,
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Date: 2014.12.19 12:03:16 -05'00'

Nina Ni, Ph.D., CMC Reviewer, Branch IV, ONDQA

B. Endorsement Block:

(See appended electronic signature page) Moojhong Rhee -S

Digitally signed by Moojhong Rhee -S
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ou=People, cn=Moojhong Rhee -S,
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Date: 2014.12.19 13:10:03 -05'00'

Moo-Jhong Rhee, Ph.D., Branch Chief, Branch IV, ONDQA

C. CC Block: entered electronically in DFS

Donna Christner, Ph.D., CMC Lead, Branch IV, ONDQA

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Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date: 22-Jul-2014

From: Donna Christner, Ph.D.
CMC Lead
DNDQA II/ONDQA

Through: Moo-Jhong Rhee, Ph.D.
Chief, Branch IV
New Drug Quality Assessment Division II
ONDQA

To: NDA 206229
Levosert (levonorgestrel-releasing Intrauterine system)

Subject: Risk Assessment

As per a new policy, each NDA with GRMP dates on or after August 1, 2014 will include a risk assessment in the Executive Summary. This will be based on an initial risk assessment that would be captured in all IQAs written for NDAs received on or after June 1, 2014. It was decided that the CMC Lead would perform a retrospective risk assessment for those NDAs received prior to June 1, 2014 that had GRMP dates after August 1, 2014,

The following IQA template was provided:

ONDQA Risk Assessment Template for Initial Quality Assessments of Original NDAs

Product attribute/CQA	Factors that can impact the CQA	Probability (O)	Severity of Effect (S)	Detectability (D)	FMECA RPN Number	Comment

In an email dated 30-May-2014, Dr. Ramesh Sood provided follow-up guidance on how to fill out the required IQA template that is used to populate the NDA template. The guidance provided templates for the most common dosage forms, but did not provide guidance for intrauterine systems. Therefore, CQAs were independently assessed.

This memo captures both the table that would normally be in the IQA and populates the first three columns of the NDA template that will be filled in by the primary CMC reviewer.

IQA RISK ASSESSMENT

Product attribute/CQA	Factors that can impact the CQA	Probability (O)	Severity of Effect (S)	Detectability (D)	FMECA RPN Number	Comment	Risk	
Assay	<ul style="list-style-type: none"> • Formulation • Raw materials • Process parameters • Scale/equipment • Site 	4	2	Release (1) Stability (3)	Release (b) (4) stability (b) (4)	Single impurity < (b) % and (b) % and Total impurities > (b) %	L	
Physical stability (solid state)					(b) (4)	(b) (4)	L	
Content Uniformity							L	
IVRT							L	
Leachables							M	
Impurities/related substances/residual solvents							Single impurity < (b) % and (b) % and Total impurities > (b) %	L
Sterility							(b) (4) OPS Micro assess	M

The evaluation from the IQA table was transferred to the following NDA table that can be used by the primary reviewer as a part of the NDA review.

NDA RISK ASSESSMENT TABLE

From Initial Quality Assessment			Review Assessment		
Product attribute/ CQA	Factors that can impact the CQA	Risk Ranking	Risk Mitigation approach	Risk Evaluation	Lifecycle Considerations / Comments
Assay	Formulation • Raw materials • Process parameters • Scale/equipment • Site	L			
Physical stability (solid state)	(b) (4)	L			
Content uniformity		L			
IVRT		L			
Leachables		M			
Impurities/ Related substances/ residual solvents		L			
Sterility		M			

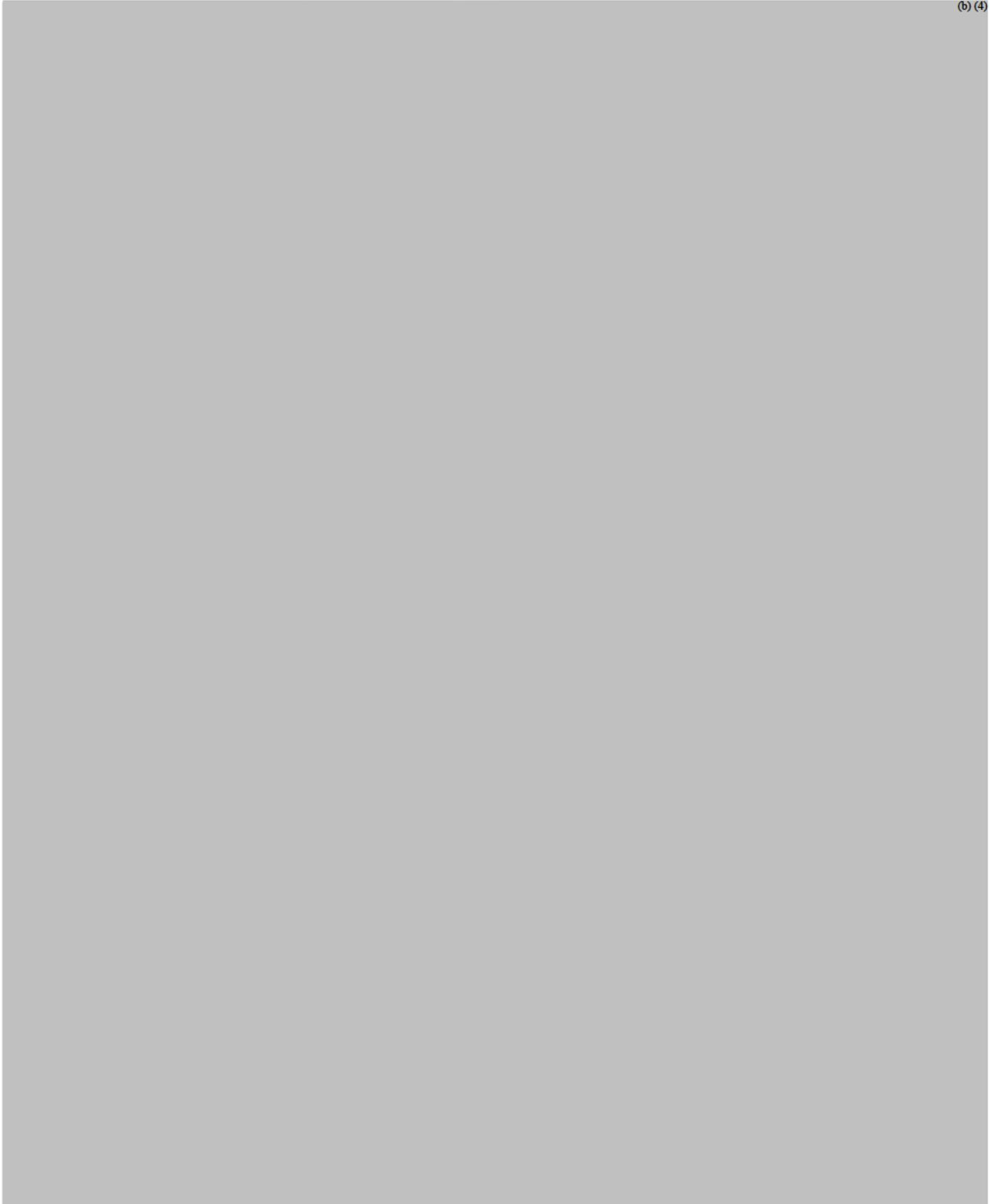
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

DONNA F CHRISTNER
07/22/2014

MOO JHONG RHEE
07/22/2014
Chief, Branch IV

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