CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206229Orig1s000

CHEMISTRY REVIEW(S)
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:

  2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page
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

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)**

<table>
<thead>
<tr>
<th>#</th>
<th>Task Name</th>
<th>Task Instructions</th>
<th>Assigned To</th>
<th>P/No</th>
<th>Act Comp</th>
<th>Task Status</th>
<th>Task Actions</th>
</tr>
</thead>
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<td>1:25</td>
<td>Application Specific: Inspection Details</td>
<td>If you are finished with the task, complete the Task Status to Complete.</td>
<td></td>
<td>3/10/15</td>
<td>MRR/04</td>
<td>Complete</td>
<td></td>
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<td>1:26</td>
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<td></td>
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<td>MRR/04</td>
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<td></td>
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<td>1:27</td>
<td>Overall Manufacturing: Inspection/Recommendations</td>
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<td>3/10/15</td>
<td>U/R/05</td>
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<td>119</td>
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<td>12/31/14</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>121</td>
<td>Order Facility Specific Criteria</td>
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<td>12/31/14</td>
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<tr>
<td>152</td>
<td>Office of Process and Product Development</td>
<td>5/31/14</td>
<td>12/31/14</td>
<td>Complete</td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>
2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page
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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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:

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

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: Lilletta® (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)
10. PHARMACOL. CATEGORY: For prevention of pregnancy for up to 3 years

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

   STRUCTURAL FORMULA:

   ![Structural Formula Image]

   MOLECULAR FORMULA: C_{21}H_{28}O_{2}
   MOLECULAR WEIGHT: 312.45
   CAS NUMBER: [797-63-7]
17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

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<th>HOLDER</th>
<th>ITEM REFERENCED</th>
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<th>COMMENTS</th>
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<td>II</td>
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<td></td>
<td>Drug Substance</td>
<td>3</td>
<td>Adequate</td>
<td>03/12/2014</td>
<td>By X. Zhang</td>
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<td>IV</td>
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<td>11/25/2014</td>
<td>By N. Ni</td>
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<td>By N. Ni</td>
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<td></td>
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<td>4</td>
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<td>III</td>
<td>III</td>
<td></td>
<td></td>
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<td>pending</td>
<td></td>
<td>Reviewed by CDRH</td>
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</table>

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:

<table>
<thead>
<tr>
<th>DOCUMENT</th>
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<th>DESCRIPTION</th>
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18. STATUS:

**ONDQA:**

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<th>DATE</th>
<th>REVIEWER</th>
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<td>Biometrics</td>
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<td>EES</td>
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<td>Pharm/Tox</td>
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<td>Biopharm</td>
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<td></td>
<td>Kelly Kitchens, Ph. D.</td>
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<td>LNC</td>
<td>NA</td>
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<td>Methods Validation</td>
<td>NA, according to the current ONDQA policy.</td>
<td>05/30/2014</td>
<td>R. Bloom, Ph. D.</td>
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<td>DMCPA</td>
<td>NA</td>
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<td>EA</td>
<td>Claim for the categorical exclusion is granted. See IQA</td>
<td>05/30/2014</td>
<td>R. Bloom, Ph. D.</td>
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<td>Microbiology</td>
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<td>Denise Miller, Ph. D.</td>
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<tr>
<td>CDRH</td>
<td>Pending</td>
<td></td>
<td>Veronica Price, Ph. D.</td>
</tr>
</tbody>
</table>
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 [03(4)], which is a well characterized synthetic progestin and has been widely used in different approved hormonal contraceptive products, including intrauterine devices. All
information related to the manufacturing and controls are referenced to Drug Master File (DMF). This DMF was previously found adequate to support the ANDA 201088 (tablets, 2013) as well as No changes are reported to the DMF since the last review. Based on this, DMF is considered adequate to support this NDA. In addition to DMF, 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 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. Each LNG drug reservoir contains 52 mg of USP grade 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 flange and pusher. The drug product and inserter tube will be packaged in a pouch constructed of and on one side, and on the other side.

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

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.
The manufacturing process for the drug product consists of [redacted]. The specification includes appearance (visual inspection), identification (HPLC), assay (HPLC), content uniformity (HPLC), degradation products (HPLC), drug release, [redacted].

The proposed specification shall be deemed 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]) and four supportive stability batches (size: [redacted] for one Phase III clinical batch and [redacted] 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] for up to 48 months and at [redacted]. 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].
- 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.
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. 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 after 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

<table>
<thead>
<tr>
<th>Attribute/ CQA</th>
<th>Factors that can impact the CQA</th>
<th>Risk Ranking*</th>
<th>Risk Mitigation approach in control strategy</th>
<th>Risk Evaluation</th>
<th>Lifecycle Considerations/ Comments**</th>
</tr>
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<tbody>
<tr>
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<td>L</td>
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<td>CMC Assessment Section</td>
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<tr>
<td>------------------------</td>
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</tr>
<tr>
<td><strong>Physical stability (solid state)</strong></td>
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<td>Particle size is controlled for drug substance</td>
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<td><strong>Content Uniformity</strong></td>
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<td>L</td>
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<td><strong>Leachables</strong></td>
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<td>Acceptable</td>
<td></td>
</tr>
<tr>
<td><strong>Impurities/related substances/residual solvents</strong></td>
<td>(b) (4)</td>
<td>L</td>
<td>Drug product is very stable</td>
<td>Acceptable</td>
<td></td>
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<tr>
<td><strong>Sterility</strong></td>
<td></td>
<td>M</td>
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<td>Acceptable</td>
<td></td>
</tr>
</tbody>
</table>

*Risk ranking applies to product attribute/CQA

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

A. Reviewer’s Signature:

(See appended electronic signature page) Nina Ni

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

B. Endorsement Block:

(See appended electronic signature page) Moojhogh Rhee

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

129 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page
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**

<table>
<thead>
<tr>
<th>Product Formulation/CQA</th>
<th>Factors that can impact the CQA</th>
<th>Probability (0)</th>
<th>Severity of Effect (3)</th>
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<th>Comment</th>
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<td></td>
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</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Product attribute/CQA</th>
<th>Factors that can impact the CQA</th>
<th>Probability (O)</th>
<th>Severity of Effect (S)</th>
<th>Detectability (D)</th>
<th>FMECA RPN Number</th>
<th>Comment</th>
<th>Risk</th>
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</table>
| Assay                 | • Formulation  
• Raw materials  
• Process parameters  
• Scale/equipment  
• Site          | 4               | 2               | Release (1) Stability (3) | [release stability](#) | [release stability](#) | Single impurity < [percentage] and Total impurities > [percentage] | L     |
| Physical stability    |                                 |                 |                        |                   |                   | (0) (4)            | L     |
| (solid state)         |                                 |                 |                        |                   |                   |                     |       |
| Content Uniformity    |                                 |                 |                        |                   |                   |                     | L     |
| IVRT                  |                                 |                 |                        |                   |                   |                     | L     |
| Leachables            |                                 |                 |                        |                   |                   |                     | M     |
| Impurities/related    |                                 |                 |                        |                   |                   |                     | L     |
| substances/residual   |                                 |                 |                        |                   |                   |                     |       |
| solvents              |                                 |                 |                        |                   |                   |                     |       |
| Sterility             |                                 |                 |                        |                   |                   |                     | 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

<table>
<thead>
<tr>
<th>Product attribute/CQA</th>
<th>Factors that can impact the CQA</th>
<th>Risk Ranking</th>
<th>Risk Mitigation approach</th>
<th>Risk Evaluation</th>
<th>Lifecycle Considerations / Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assay</td>
<td>Formulation</td>
<td>L</td>
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<tr>
<td>Physical stability (solid state)</td>
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<td>L</td>
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<tr>
<td>Content uniformity</td>
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<td>L</td>
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<tr>
<td>IVRT</td>
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<tr>
<td>Leachables</td>
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<td>M</td>
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</tr>
<tr>
<td>Impurities/Related substances/residual solvents</td>
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<tr>
<td>Sterility</td>
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<td>M</td>
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</tbody>
</table>
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