PRODUCT QUALITY REVIEW(S)
Recommendation: Approve

NDA 22075 (resubmission)

Review # 2

<table>
<thead>
<tr>
<th>Drug Name/Dosage Form</th>
<th>Nourianz® (istradefylline) tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strength</td>
<td>20 mg, 40 mg</td>
</tr>
<tr>
<td>Route of Administration</td>
<td>Oral</td>
</tr>
<tr>
<td>Rx/OTC Dispensed</td>
<td>Rx</td>
</tr>
<tr>
<td>Applicant</td>
<td>Kyowa Kirin, Inc</td>
</tr>
<tr>
<td>US agent, if applicable</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Quality Review Team

<table>
<thead>
<tr>
<th>DISCIPLINE</th>
<th>REVIEWER</th>
<th>SECONDARY REVIEWER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug Substance</td>
<td>Rohit Tiwari</td>
<td>Su Tran</td>
</tr>
<tr>
<td>Drug Product/Labeling</td>
<td>Andrei Ponta</td>
<td>Wendy Wilson-Lee</td>
</tr>
<tr>
<td>Manufacturing</td>
<td>Yuesheng Ye</td>
<td>Yaodong (Tony) Huang</td>
</tr>
<tr>
<td>Biopharmaceutics</td>
<td>Gerlie Gieser</td>
<td>Ta-Chen Wu</td>
</tr>
<tr>
<td>Regulatory Business Process Manager</td>
<td>Dahlia A. Walters</td>
<td>--</td>
</tr>
<tr>
<td>Application Technical Lead</td>
<td>Martha Heimann</td>
<td>--</td>
</tr>
<tr>
<td>Laboratory (OTR)</td>
<td>N/A</td>
<td></td>
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<tr>
<td>ORA Lead</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Environmental Analysis (EA)</td>
<td>N/A</td>
<td></td>
</tr>
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Amendments Reviewed

<table>
<thead>
<tr>
<th>SUBMISSIONS REVIEWED</th>
<th>DOCUMENT DATE</th>
<th>DISCIPLINE(S) AFFECTED</th>
</tr>
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<tbody>
<tr>
<td>SD-061, Resubmission after CR</td>
<td>2/27/2019</td>
<td>All</td>
</tr>
<tr>
<td>SD-065, Response to IR</td>
<td>4/12/2019</td>
<td>Biopharmaceutics</td>
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<tr>
<td>SD-068, Response to IR</td>
<td>5/14/2019</td>
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<td>SD-072, Response to IR</td>
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<td>SD-073, Container-Carton Labels</td>
<td>6/21/2019</td>
<td>Product/Labeling</td>
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<tr>
<td>SD-075, Response to IR</td>
<td>6/28/2019</td>
<td>Product, Biopharmaceutics</td>
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</table>
Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

<table>
<thead>
<tr>
<th>DMF #</th>
<th>Type</th>
<th>Holder</th>
<th>Item Referenced</th>
<th>Status</th>
<th>Date Review Completed</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>III</td>
<td>(b)</td>
<td></td>
<td>(b) (4)</td>
<td>N/A 1</td>
<td>N/A 1</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>(b)</td>
<td></td>
<td>(b) (4)</td>
<td>N/A 1</td>
<td>N/A 1</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>(b)</td>
<td></td>
<td>(b) (4)</td>
<td>N/A 1</td>
<td>N/A 1</td>
<td></td>
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<tr>
<td>III</td>
<td>(b)</td>
<td></td>
<td>(b) (4)</td>
<td>N/A 1</td>
<td>N/A 1</td>
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<tr>
<td>IV</td>
<td></td>
<td></td>
<td></td>
<td>N/A 1</td>
<td>N/A 1</td>
<td></td>
</tr>
</tbody>
</table>

1 Adequate information in application.

B. Other Documents: IND, RLD, or sister applications

<table>
<thead>
<tr>
<th>DOCUMENT</th>
<th>APPLICATION NUMBER</th>
<th>DESCRIPTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>IND</td>
<td>58356</td>
<td>Development of istradefylline tablets for adjunctive treatment of Parkinson’s disease.</td>
</tr>
</tbody>
</table>

2. CONSULTS: N/A
Executive Summary

I. Recommendations and Conclusion on Approvability

The Office of Product Quality (OPQ) review team recommends that the Agency **Approve** NDA 22075 for Nouri anz (istradefylline) tablets. From a quality perspective, the application, as amended, provides adequate information to ensure that the applicant can consistently manufacture a product that is suitable for use by the intended patients.

II. Summary of Quality Assessments

A. Product Overview

Istradefylline (KW-6002), a new molecular entity, is a novel and selective adenosine A2A receptor antagonist developed by Kyowa Kirin for use as adjunctive treatment to levodopa/carbidopa in adult patients with Parkinson’s disease (PD) experiencing “OFF” time. The applicant submitted the original NDA for istradefylline tablets in 2007. A “Not Approvable” (NA) letter was issued on 2/25/2008 due to clinical deficiencies. There were no outstanding quality issues. After extended discussions between the applicant and FDA, and additional efficacy studies, the NDA was resubmitted on 2/27/2019. The current review focuses on manufacturing changes (e.g., site changes, process modifications, etc.) implemented after the 2008 NA action and additional quality information and controls consistent with current FDA and ICH recommendations.

<table>
<thead>
<tr>
<th>Proposed Indication(s) including Intended Patient Population</th>
<th>Adjunctive treatment to levodopa/carbidopa in adult patients with Parkinson's disease (PD) experiencing &quot;OFF&quot; episodes.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of Treatment</td>
<td>Chronic</td>
</tr>
<tr>
<td>Maximum Daily Dose</td>
<td>40 mg</td>
</tr>
<tr>
<td>Alternative Methods of Administration</td>
<td>None</td>
</tr>
</tbody>
</table>

B. Quality Assessment Overview

*Drug Substance*

The bulk active pharmaceutical ingredient (API), istradefylline, is a well characterized, small molecule that is essentially insoluble (< 1 µg/mL) in aqueous media across the pH range 2.0 to 12.0. The bulk drug substance is manufactured by Kyowa Pharma Chemical, which replaces the original manufacturing site, Kyowa Hakko Kirin-Sakai. The applicant provided adequate comparability information in the resubmission to bridge the drug substance from the two sources. The information provided, which includes a comparison of manufacturing processes, batch release data, and stability data for 3 drug substance batches from the new source and more than 3 batches from the previous source, is deemed acceptable.
Additional information submitted by the applicant includes justification of regulatory starting materials (per ICH Q11), a risk assessment for elemental impurities (per ICH Q3D), and assessment of potential genotoxic impurities (PGIs, per ICH M7), and an updated drug substance specification that includes appropriate controls for critical quality attributes, including identity, strength, and purity. Based on the information provided, the applicant has adequately justified omission of testing for elemental impurities and PGIs in the drug substance. The applicant also proposes deletion of the $D(v, 0.5)$ acceptance criterion for particle size and retaining the $D(v, 0.9)$ criterion. This is justified by manufacturing experience, as istradefylline has been marketed in Japan since 2013. The proposed 6 month retest period is supported by data provided.

**Drug Product**

Nourianz tablets are immediate-release, peach-colored, film-coated tablets that contain 20 mg or 40 mg istradefylline. The tablets are compositionally proportional and contain the following excipients: lactose monohydrate, microcrystalline cellulose, crospovidone, polyvinyl alcohol, and magnesium stearate. Tablet compositions are unchanged from the original NDA. Nourianz tablets will be packaged in 90-count high-density polyethylene bottles with aluminum foil liners and closures for commercial distribution.

The manufacturing process for Nourianz tablets includes the following unit operations: The manufacturing process and batch scale are unchanged from the original NDA submission and are deemed acceptable.

The final drug product specification reflects revisions proposed by the applicant in the resubmission or requested by the Agency during the review. The principal changes are: 1) revision of the limits for specified impurities to not more than (NMT)$^{(b)(4)}$ % consistent with the ICH qualification threshold for the 40 mg maximum daily dose; and 2) revision of the dissolution method to provide for testing at 20 minutes rather than 15 minutes as originally proposed. The change to the dissolution time point is based on dissolution profile data from Phase 3 clinical batches, and primary stability and process validation batches for commercial image tablets.

Overall, the comparative *in vitro* dissolution profile data and the *in vivo* bioequivalence data provided for the 20 mg and 40 mg strengths are adequate to establish the bridge between the drug product used in the pivotal Phase 3 clinical trials and the final proposed to-be-marketed drug product.

Based on the stability data provided in the resubmission, which includes up to 60 months of long-term data for primary stability batches, the requested 60-month expiration dating period for product stored under controlled room temperature conditions is granted.
Facilities

All facilities that will be involved in commercial manufacture and testing of istradefylline and Nourianz (istradefylline) tablets are currently acceptable.

Environmental Assessment

The applicant submitted a claim for categorical exclusion under 21 CFR § 25.31(b). Approval of the application is expected to increase use of the active moiety; however, the expected environmental introduction concentration (EIC) is less than 1 part per billion and there are no extraordinary circumstances. The claim is granted.

C. Special Product Quality Labeling Recommendations

There are no special labeling recommendations.

D. Final Risk Assessment

When the original NDA was reviewed and recommended for approval from a quality perspective, formal risk assessment was not part of the review process. Given the limited changes in the resubmission, risk assessment is not deemed necessary.
LABELING

I. Package Insert

1. Highlights of Prescribing Information

<table>
<thead>
<tr>
<th>Item</th>
<th>Information Provided in NDA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Product Title (Labeling Review Tool and 21 CFR 201.57(a)(2))</td>
<td>Nourianz (istradefylline) tablets, for oral use</td>
</tr>
<tr>
<td>Proprietary name and established name</td>
<td>Nourianz (istradefylline) tablets, for oral use</td>
</tr>
<tr>
<td>Dosage form, route of administration</td>
<td>Tablets, oral</td>
</tr>
<tr>
<td>Controlled drug substance symbol</td>
<td>NA</td>
</tr>
<tr>
<td>Dosage Forms and Strengths (Labeling Review Tool and 21 CFR 201.57(a)(8))</td>
<td>Tablets: 20 mg and 40 mg</td>
</tr>
</tbody>
</table>

Is the information accurate? ☒ Yes ☐ No

2. Section 2 Dosage and Administration

2. DOSAGE AND ADMINISTRATION

2.1 Dosing Information

The recommended dose of NOURIANZ is 20 mg administered orally, once a day. The dose may be increased to 40 mg once daily. Initial dose titration is not required.

NOURIANZ can be taken with or without food [see Clinical Pharmacology (12.3)]

<table>
<thead>
<tr>
<th>Item</th>
<th>Information Provided in NDA</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12))</td>
<td>None</td>
</tr>
</tbody>
</table>

Is the information accurate? ☒ Yes ☐ No

3. Section 3 Dosage Forms and Strengths
3 DOSAGE FORMS AND STRENGTHS

- 20 mg tablets: Peach-colored, pillow-shaped, film-coated tablets with “20” debossed on one side.
- 40 mg tablets: Peach-colored, almond-shaped, film-coated tablets with “40” debossed on one side.

<table>
<thead>
<tr>
<th>Item</th>
<th>Information Provided in NDA</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Refer to Labeling Review Tool and 21 CFR 201.57(c)(4))</td>
<td></td>
</tr>
<tr>
<td>Available dosage forms</td>
<td>Tablets</td>
</tr>
<tr>
<td>Strengths: in metric system</td>
<td>20 mg and 40 mg</td>
</tr>
<tr>
<td>Active moiety expression of strength with equivalence statement</td>
<td>istradefylline</td>
</tr>
<tr>
<td>A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.</td>
<td>Peach-colored, pillow-shaped, film-coated tablet, with “20” debossed on one side OR Peach-colored, almond-shaped, film-coated tablet, with “40” debossed on one side</td>
</tr>
</tbody>
</table>

Is the information accurate? ☑ Yes  ☐ No

4. Section 11 Description

11 DESCRIPTION

NOURIANZ contains istradefylline, an adenosine receptor antagonist which has a xanthine derivative structure. The chemical name is (E)-8-(3,4-dimethoxystyryl)-1,3-diethyl-7-methyl-3,7-dihydro-1H-purine-2,6-dione. Its molecular formula is C_{20}H_{24}N_{4}O_{4}. The molecular weight is 384.43. Istradefylline has the following structural formula:

![Istradefylline structure](image)

Istradefylline is a light yellow-green crystalline powder. Istradefylline has a dissociation constant (pK_\text{a}) of 0.78. The aqueous solubility of istradefylline is ~0.5 μg/mL across the physiological pH range, and 0.6 μg/mL in water.

NOURIANZ tablets are intended for oral administration only. Each tablet contains 20 mg or 40 mg istradefylline and the following inactive ingredients: lactose monohydrate, microcrystalline cellulose, crospovidone, polyvinyl alcohol, and magnesium stearate. The film coating contains hypromellose, lactose monohydrate, titanium dioxide, polyethylene glycol 3350, triacetin and the following dye: iron oxide yellow and iron oxide red. Carnauba wax is used for polishing.

<table>
<thead>
<tr>
<th>Item</th>
<th>Information Provided in NDA</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12), 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv))</td>
<td></td>
</tr>
<tr>
<td>Proprietary name and established name</td>
<td>Nourianz (istradefylline) tablets, for oral use</td>
</tr>
<tr>
<td>Dosage form and route of administration</td>
<td>Tablets: 20 mg and 40 mg</td>
</tr>
</tbody>
</table>
### QUALITY ASSESSMENT

| Active moiety expression of strength with equivalence statement (if applicable) | istradefylline |
| For parenteral, otic, and ophthalmic dosage forms, include the quantities of all inactive ingredients [see 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv)], listed by USP/NF names (if any) in alphabetical order (USP <1091>) | lactose monohydrate, microcrystalline cellulose, crospovidone, polyvinyl alcohol, and magnesium stearate, and hypromellose, lactose monohydrate, triacetin, titanium dioxide, PEG 3350, iron oxide yellow, iron oxide red |
| Statement of being sterile (if applicable) | Not applicable |
| Pharmacological/therapeutic class | Adenosine receptor antagonist |
| Chemical name, structural formula, molecular weight | C_{20}H_{24}N_{4}O_{4} – 348.43 g/mol |
| If radioactive, statement of important nuclear characteristics. | Not applicable |
| Other important chemical or physical properties (such as pKa or pH) | It’s a light yellow-green powder with a pKa of 7.8 and a solubility of 0.6 µg/mL in water. |

**Is the information accurate?** ☑ Yes ☐ No

### 5. Section 16 How Supplied/Storage and Handling

**16 HOW SUPPLIED/STORAGE AND HANDLING**

NOURLIANZ (istradefylline) tablets are available as:

**20 mg Tablet:**
Peach-colored, pillow-shaped, film-coated tablets with “20” debossed on one side.
Bottle of 90: NDC 42747-602-90

**40 mg Tablet:**
Peach-colored, almond-shaped, film-coated tablets with “40” debossed on one side.
Bottle of 90: NDC 42747-604-90

**Storage**
Store at 20°C to 25°C (68°F-77°F); excursions permitted between 15°C and 30°C (59°F-86°F) [see USP Controlled Room Temperature].
QUALITY ASSESSMENT

<table>
<thead>
<tr>
<th>Item</th>
<th>Information Provided in NDA</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Refer to Labeling Review Tool and 21 CFR 201.57(c)(17))</td>
<td>Tablets: 20 mg and 40 mg</td>
</tr>
<tr>
<td>Strength of dosage form</td>
<td>Tablets: 20 mg and 40 mg</td>
</tr>
<tr>
<td>Available units (e.g., bottles of 100 tablets)</td>
<td>20 mg: bottles of 90 tablets, (b) (4) 40 mg: bottles of 90 tablets, (b) (4)</td>
</tr>
<tr>
<td>Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number</td>
<td>Peach-colored, pillow-shaped, film-coated tablet, with “20” debossed on one side OR Peach-colored, almond-shaped, film-coated tablet, with “40” debossed on one side</td>
</tr>
<tr>
<td>Special handling</td>
<td>Not Applicable</td>
</tr>
<tr>
<td>Storage conditions</td>
<td>USP controlled room temperature</td>
</tr>
<tr>
<td>Manufacturer/distributor name (21 CFR 201.1(h)(5))</td>
<td>Kyowa Pharamaceuticals, INC.</td>
</tr>
</tbody>
</table>

**Reviewer’s Assessment of Package Insert: Adequate**

Prescribing Information complies with all regulatory requirements from a CMC perspective.
However, some revisions have been identified and will be communicated to the Applicant as part of DNP labeling negotiations.

II. Labels:

1. **Bottle Labels**

1 Page(s) of Draft Labeling has been Withheld in Full as B4 (CCI/TS) immediately following this page
<table>
<thead>
<tr>
<th>Item</th>
<th>Information provided in the bottle label</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))</td>
<td>Nourianz (istradefylline) tablets, for oral use</td>
</tr>
<tr>
<td>Dosage strength</td>
<td>Complies</td>
</tr>
<tr>
<td>Net contents</td>
<td>Complies</td>
</tr>
<tr>
<td>“Rx only” displayed prominently on the main panel</td>
<td>Complies</td>
</tr>
<tr>
<td>NDC number (21 CFR 207.35(b)(3)(i))</td>
<td>Complies</td>
</tr>
<tr>
<td>Lot number and expiration date (21 CFR 201.17)</td>
<td>Complies</td>
</tr>
<tr>
<td>Storage conditions</td>
<td>Complies</td>
</tr>
<tr>
<td>Bar code (21 CFR 201.25)</td>
<td>Complies</td>
</tr>
<tr>
<td>Name of manufacturer/distributor</td>
<td>Complies</td>
</tr>
<tr>
<td>And others, if space is available</td>
<td>Not Applicable</td>
</tr>
</tbody>
</table>

**Reviewer’s Assessment of Labels: Adequate**

OPQ-XOPQ-TEM-0001v05       Page 6 of 7       Effective Date: October 15, 2017
The container labels comply with regulatory requirements from a CMC perspective. It bears the “Rx only” statement, the NDC number, name of manufacturer, net contents, strength, and the name (proprietary and established).

List of Suggested Edits Communicated to Applicant:

1. Ensure that the excipients are listed in alphabetical order in the PI.

Overall Assessment and Recommendation: Adequate

Primary Labeling Reviewer Name and Date: Andrei Ponta, Ph.D. 1-Jul-2019
QUALITY ASSESSMENT

BIOPHARMACEUTICS

Product Background:

**NDA:** 022075  
**Drug Product Name / Strength:** Istradefylline Tablets / 20 mg, 40 mg  
**Route of Administration:** Oral  
**Proposed Indication:** For adjunctive treatment to levodopa/carbidopa in adult patients with Parkinson’s disease (PD) experiencing “OFF” episodes  
**Proposed Dosage:** 20 mg orally once daily; may be increased to 40 mg once daily based on therapeutic response; administer with or without food  
**Applicant Name:** Kyowa Kirin, Inc.  
**Primary Reviewer:** Gerlie Gieser, Ph.D.  
**Secondary Reviewer:** Ta-Chen Wu, Ph.D.

**Review Recommendation: APPROVAL**

**Review Summary:**  
**Dissolution method and acceptance criterion**  
The proposed dissolution method and the revised acceptance criterion (as tabulated below) are recommended for the routine QC of Istradefylline Tablets 20 mg and 40 mg at batch release and during stability testing.

<table>
<thead>
<tr>
<th>USP Apparatus</th>
<th>Speed</th>
<th>Medium</th>
<th>Volume</th>
<th>Acceptance criterion</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 (paddle), with JP sinker</td>
<td>50 rpm</td>
<td>0.5% sodium lauryl sulfate (SLS) in deionized water 37 ± 0.5°C</td>
<td>900 mL</td>
<td>NLT (80% (Q) of the label claim dissolved in 20 min)</td>
</tr>
</tbody>
</table>

**Bridging to the To-Be-Marketed Drug Product**  
Overall, the comparative *in vitro* dissolution profile data and the *in vivo* BE data provided for the 20 mg and 40 mg strengths are adequate to establish the bridge between the drug product used in the pivotal Phase 3 clinical trials and the final proposed to-be-marketed drug product.

*Note that the above recommendations/conclusions may be revisited should additional clinical trials/studies be required by FDA to support NDA approval.

**List of Submissions reviewed:**  
SDN-61, 2/27/2019 (Complete Response to FDA 2008 Action Letter)  
SDN-65, 4/12/2019 (Response to Early Biopharmaceutics Information Request)  
SDN-75, 6/28/2019 (Response to Quality/Biopharmaceutics Information Request)
Concise Description of Outstanding Issues:
None

**BCS Designation**

The Applicant considers [and the Office of Clinical Pharmacology and Biopharmaceutics (OCPB) Reviewer of the original NDA classified] istradefylline as a BCS II (low solubility, high permeability) drug substance.

**Reviewer’s Assessment:**

**Solubility:** Low
The drug substance is provided by the API supplier as (b) (4). API (b) (4) are insoluble in aqueous media regardless of pH. Figure 1 shows that API (b) (4) both exhibit *numerically* higher solubility values in media with lower pH, (b) (4).

![Figure 1. Solubility Profiles of Istradefylline in Aqueous Media with Varying pH, and Varying Levels of Surfactant, at 37 °C](image)

**Permeability:** Possibly High
Per the OCPB Review of the original NDA, the absolute bioavailability of istradefylline oral tablets is not known but a between-study comparison of the AUC0–∞ of istradefylline indicated a relative bioavailability of 112% for the 40-mg intended commercial tablet, compared to the oral suspension.

Also, the *in vitro* transport study using the Caco-2 cell line showed that the permeability coefficient of [14C]-istradefylline was comparable to that of propranolol, a highly permeable drug.

**Dissolution:** Not Rapid (in medium without added surfactant)
The cumulative dissolution of istradefylline tablets is low regardless of medium pH, i.e., <20% in various pH buffers and water; (b) (4) (b) (4) For the dissolution profiles of istradefylline tablets in various pH...
media in the absence and presence of surfactant, refer to Figures P.2.2.1.2-1 to P.2.2.1.2-5 of the Pharmaceutical Development Report (PDR).

Dissolution Method and Acceptance Criteria

Reviewer’s Assessment:

Dissolution Method - ADEQUATE

Per the OCPB and CMC Reviews of the original NDA, the proposed dissolution method [consisting of USP Apparatus 2 (paddle) at 50 rpm with JP sinker, and 900 mL of 0.5% sodium lauryl sulfate (SLS) in deionized water at 37°C] achieved sufficient discriminating power and sink conditions, and thus was deemed adequate.

Specifically, the proposed dissolution method was demonstrated to be discriminating for changes in the levels of ; see Figures P.2.2.1.2-12 to -18 of the Pharmaceutical Development Report (PDR).

Per the Applicant, the use of a JP sinker Based on the supplementary analytical method validation results provided for the HPLC method when using JP sinker during dissolution testing of the tablets with the final shape and film coating color, the Applicant concluded that the analytical method meets the pre-specified acceptance criteria for system suitability, accuracy, specificity, repeatability and intermediate precision of the dissolution data collected at min. Previously, the HPLC (with UV detection at 235 nm) method was also validated for linearity, range, robustness (with respect to HPLC parameters), filter compatibility (0.45 µm Nylon, PTFE, PVDF and Polysulfone 25 mm diameter), and stability of solutions. The Dissolution Test Procedure highlights the need for all standard and sample solutions to be prepared and analyzed under red light conditions or under yellow light conditions to eliminate the spectral distribution below 450 nm. When protected from light, the sample and standard solutions were reported to be stable for up to 3 days and 4 days, respectively, at room temperature or at 4°C.

Dissolution Acceptance Criteria – REVISED ACCEPTANCE CRITERIA ADEQUATE

The proposed dissolution acceptance criterion is ‘NLT (%) of the labeled amount of istradefylline is dissolved in minutes’. Figure 2 shows the Applicant’s dissolution profiles of drug product lots used in pivotal/supportive clinical trials, primary stability, process validation, and commercial image tablets.

This Reviewer’s recommended dissolution acceptance criterion for QC testing of both strengths at batch release and during stability testing is “NLT (%) at 20 min”, based mainly on the in vitro dissolution profiles of the ‘Tablet B’ and ‘Tablet B Commercial’ drug product lots used in either Phase 3 clinical trials or in the BE study in Figure 2. Additionally, the Reviewer’s recommended acceptance criterion considers the following factors:
QUALITY ASSESSMENT

a. Setting the Q = (4)% at 20 min rather than at min is deemed appropriate because 20 min is anticipated to be more efficient in terms of ability to reject drug product lots manufactured with either API (see Table P.2.2.1.1-4 and Figure P.2.2.1.1.2 of the PDR), or higher-than-target tablet film coating weight gain (see Figure P.2.2.1.1-11 of the PDR).

b. 20 min would ensure that all three drug product lots demonstrated to be bioequivalent in BE Study 6002-US-022 would pass routine QC dissolution testing (see Figure P.2.2.1.2-19 of the PDR).

c. for the attainment of the target cumulative dissolution of NLT (4)% Note that both the 20 min and min time points lie within the plateau of the cumulative dissolution curve, and have comparable % RSD (data variability).

d. Based on the proposed package insert and the OCPB Review of the original NDA, there was no QT prolonging effect observed in subjects enrolled in clinical pharmacology studies including the Thorough QT Study.

Figure 2
Dissolution Profiles of Drug product Lots used in Pivotal/Supportive Clinical Trials, Primary Stability, Process Validation, and Commercial Image Tablets that were Analyzed Using the Proposed Dissolution Method (with JP Sinkers)
QUALITY ASSESSMENT

40 mg Tablets

USP Apparatus 2 with JP sinker, 900 mL of 0.5% SLS medium, 50 rpm, 37°C
(n=6, however, lot 0588-A, 0589-A and 0590-A was evaluated n=18)

In Figure 1 above:
1. “Tablet B” Lots KVMN (20 mg) and KPKW (40 mg) were both used in Phase 3 Study 6002-014. Lot KPKW (batch size kg) was also used in Clinical Pharmacology Studies 6002-017 (abuse potential), 6002-016 (hepatic impairment), and 6002-015 (DDI w/ rifampin).
2. “Tablet B Commercial” lots have ID numbers beginning with “C”. Lot C4J0260 (20 mg) was used in Phase 3 Study 6002-US-025 whereas Lot C4J0261 (40 mg) was used in BE Study 6002-US-022; both lots were manufactured a kg scale and were also used in registration stability studies. All other “Tablet B Commercial” lots were used in either registration stability or process validation studies.
3. The final commercial image/final API supplier lots of 20 mg and 40 mg are represented by Lots WFCD and XMDT, respectively.

Dissolution Profiles of the Phase 3 Clinical Trial Lots and the Primary Registration Batches During Long-term Storage

Per the Applicant, the clinical trial lots were up to 48 months old at the time of clinical trial use. Based on the provided dissolution profile data for the Phase 3 clinical trial lots during 48 months of long-term storage (generated using the final proposed QC dissolution method), the Phase 3 clinical trial (Tablet B or Tablet B Commercial) lots would be able to conform to this Reviewer’s recommended acceptance criterion (Q = % at 20 min) by USP Stage 1 or 2 testing over the duration of their clinical trial use (see Figure 3).

There were no apparent trends in the dissolution profiles of the two “Tablet B Commercial” lots that were used in clinical (BE or Phase 3) studies and registration stability studies over 60 months of long-term storage, regardless of packaging configuration (bottle); see Figure 4.
The green horizontal dashed line (- - -) represents the target lower limit of dissolution (i.e., $Q = \frac{75}{140}$) whereas the blue vertical dashed line (- - -) is the cut-off/demarcation line for 20 minutes of dissolution testing.
“Tablet B Commercial” Lot C4J0260 (20 mg) was used in Phase 3 US-025 whereas “Tablet B Commercial” Lot C4J0261 (40 mg) was used in BE Study 6002-US-022. The bottle packaging configurations of both lots were also evaluated in primary registration stability studies.

The green horizontal dashed line (- - -) represents the target lower limit of dissolution (i.e., $Q = \frac{(b)}{(4)}$) whereas the blue vertical dashed line (---) is the cut-off/demarcation line for 20 minutes of dissolution testing.

**Impact of API particle size on Dissolution**

Note that API is used for tablet manufacture; the proposed particle size is $D_{(v,0.9)} \leq \frac{(b)}{(4)} \mu m$, by Laser Diffraction. Based on the comparative dissolution profile data provided for 20 mg tablets manufactured using API (Figure P.2.2.1.1-2 and Table P.2.2.1.1-4 of the PDR/Drug Product), the Applicant’s proposed API $D_{90}$ of $\leq \frac{(b)}{(4)} \mu m$ appears reasonable. Note that the Drug Substance Reviewer (Dr. Rohit Tiwari) considers the proposed API particle size specification to be acceptable.

**Impact of API Polymorphic Form on Solubility**

Under certain conditions, API can potentially convert to any of four additional polymorphic forms (including ). Figure 1 shows that polymorphic conversion of API does not significantly impact the drug substance’s already low solubility profile in various pH media. Per the Drug Product Reviewer (Dr. Andrei Ponta), there was no API polymorphic change observed over 60 months of long-term stability testing of the tablets; thus, polymorphic testing for API is not required to be added to the Finished Product QC Specifications.

**Impact of on Dissolution**

The Applicant indicated that the observed did not impact appearance, assay, impurities/degradants, dissolution, and hardness values, which all remained well within the specified range. Figure 3 above confirms that there was no apparent storage time-dependent change in dissolution profiles of the packaged tablets. Per the recommendation of Dr. Ponta, “” (NMT
% was added to the release and shelf-life/stability QC specifications of the finished product.

On 6/28/2019, the Applicant agreed to tighten the dissolution acceptance criterion per FDA recommendation, and revised pertinent NDA documents accordingly.

**Bridging of Clinical Formulations (‘Tablet B’ and ‘Tablet B Commercial’) to the Final To-Be-Marketed Tablet**

**Reviewer’s Assessment: ADEQUATE**

The drug product (“Tablet B”) evaluated in pivotal Phase 2b/3 clinical trials (Studies 6002-US-005, 6002-US-006, 6002-US-013, 6002-0608, 6002-009, 6002-US-018, 6002-EU-007 and 6002-014) and several earlier clinical studies (e.g., DDI/BE/PK in organ impairment Studies 015/Rifampin, 016/hepatic impairment, 026/Digoxin, 011/food-effect, 012/BE 10 vs 20 mg) has the same dosage form and tablet core formulation composition and manufacturing process steps (etc.) as the “Tablet B Commercial” evaluated in primary registration/process validation studies. Additionally, the manufacturing site/scale of at least some of the Phase 3 clinical tablets are the same as those of the primary registration/validation lots, as well as the final commercial image tablets (i.e., kg, respectively).

The final proposed to-be-marketed drug product differ only from the “Tablet B Commercial” tablets in terms of appearance (with debossing on one side only) and the API supplier (Kyowa Pharma Chemical/KPC instead of KHK).

Note that for the manufacture of ‘Tablet B’, ‘Tablet B Commercial’ and the ‘Final Commercial’ drug product, either drug substance/API manufacturing Process was used. The final commercial API Process is KPC is the final commercial API supplier whereas KHK was the API supplier for the API material. Apart from the manufacturing site change (from KHK to KPC), the only other differences between API Processes are the

In Vivo Bridging of ‘Tablet B’ to Tablet B Commercial:

The results of BE Study 6002-US-022 demonstrate the lack of an effect on in vivo PK of the changes in (40 mg) tablet appearance (shape, debossing) and film coat composition, as well as the changes in API supplier/scale/process, tablet manufacturing site and batch scale up, that were introduced during clinical development, i.e., “Tablet B” = “Tablet B Commercial”. (The in vivo PK results of Study 6002-US-022 --- as confirmed by the OCP Reviewer of the original NDA --- are consistent with the Applicant’s observation that all three tested lots in the BE study had similar dissolution profiles by f2 analysis.)

Note that the 20 mg strength (“Tablet B Commercial”) was used in Phase 3 Study 6002-US-025, and PK data are available for 20 mg “Tablet B” from other studies (e.g., 6002-
0205, -012, -011/Food-Effect,-0205, -002, -9703, -0104, -DDI w/midazolam). Note also the the 20 mg and 40 mg strengths of “Tablet B Commercial” are compositionally proportional; thus, this Reviewer considers that it is appropriate to extend to the lower strength the BE conclusions of Study 6002-US-022 generated using the higher strength.

In Vitro Bridging of ‘Tablet B’, ‘Tablet B Commercial’ and the Final Commercial Tablet

Figure 1 shows that the lots representing Tablet B (used in Clinical Studies), Tablet B Commercial (used in Clinical/Registration Stability/Process Validation) and the Final Commercial [Image] Tablet Drug Product have similar dissolution profiles. [That the Applicant’s calculated $f_2$ values demonstrate similarity of the final commercial 40 mg tablets to ‘Tablet B’ Lot C3K0019 and ‘Tablet B Commercial’ Lot C4J0261 (but not to the ‘Tablet B’ Lot F0946001) evaluated in BE Study 6002-US-022 suggests that in vitro dissolution testing is possibly sensitive to 40 mg tablet batch scale differences that may not necessarily be clinically relevant; see Tables 14 and 15 of SDN-65. Thus, this Reviewer suggests that for the evaluation of future post-approval CMC changes involving the 40 mg tablet strength, Clinical Lots C3K0019 and C4J0261 (both produced at kg scale) be used as reference/pre-change drug product(s).]

Consistent with the “Tablet B Commercial” tablets used in either the BE or Phase 3 clinical trial (see Figure 3 above), there were no trends in dissolution profile on stability observed with the final to-be-marketed drug product lots (20 mg WFCD and 40 mg XMDT) manufactured with the final commercial image and the final proposed commercial API supplier over 24 months of long-term stability testing (refer to Figure 5 below), regardless of packaging configuration (bottle).

In Vitro Bridging of the US Phase 3 ‘Tablet B’ to Japanese Phase 3 ‘Tablet B’:
The ‘Tablet B’ used in US Phase 3 studies differ from the ‘Tablet B’ used in Japanese Phase 3 trials only in terms (b) (4) of the tablets. The similarity of the dissolution profiles (i.e., $f_2$>50; (see Table P.2.2.1-5 and Figure P.2.2.1-1 of the PDR) confirmed the equivalence of the lots used in US and Japanese Phase 3 clinical trials. Note that unlike the US trials, the Japanese Phase 3 clinical trials used only the 20 mg (not the 40 mg) tablets.

Note that the Applicant does not plan to commercialize the 10 mg strength.

Impact of over-encapsulation of ‘Tablet B’ on dissolution:
The over-encapsulation of Lot C3K0015 for blinding purposes in Study 6002-EU-007 did not adversely impact the very rapid dissolution profile of the tablet in the proposed dissolution medium; see Figure P.2.2.1.2-20 of the PDR.
Biowaiver Request

Reviewer’s Assessment: NOT APPLICABLE

A biowaiver was not requested nor required because both 20 mg and 40 mg strengths of the tablets manufactured using the proposed commercial formulation/process were evaluated for PK (or shown to be BE in terms of PK to those evaluated for) clinical efficacy & safety, as well as stability; refer to PK data provided for ‘Tablet B’ and ‘Tablet B Commercial’. Additionally, note that in vitro bridging data were provided to qualify the CMC changes (in the API supplier and tablet appearance) made to ‘Tablet B Commercial’ which do not warrant conducting a BE study.
Gerlie Gieser
Digitally signed by Gerlie Gieser
Date: 7/25/2019 03:29:55PM
GUID: 507592ba00003d190b2ea34fe8fb8ccb

Ta-Chen Wu
Digitally signed by Ta-Chen Wu
Date: 7/25/2019 03:44:31PM
GUID: 508da6df00269e151ff37cd8f4e13a1
NDA 22-075

Istradefylline Tablets

Kyowa Pharmaceutical, Inc.

Wendy I. Wilson, Ph.D.
Office of New Drug Quality Assessment
for the Division of Neurology Drug Products
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CHEMISTRY REVIEW

Chemistry Review Data Sheet

CHEMISTRY REVIEW

1. NDA:  22-075

2. REVIEW #:  01


4. REVIEWER:  Wendy I. Wilson, Ph.D.

5. PREVIOUS DOCUMENTS:

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6. SUBMISSION(S) BEING REVIEWED:

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<td>21-JAN-2008</td>
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<tr>
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<td>30-JAN-2008</td>
</tr>
<tr>
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7. NAME & ADDRESS OF APPLICANT:

Name: Kyowa Pharmaceutical, Inc.
Address: 212 Carnegie Center, Suite 101, Princeton, NJ 08540
Representative: Lieselotte Bloss, DVM
Telephone: 609-919-1100

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name:  (tentative)
b) Non-Proprietary Name (USAN):  Istradefylline
c) Code Name/# (ONDQA only):  KW-6002
d) Chem. Type/Submission Priority (ONDQA only):
   • Chem. Type:  1
   • Submission Priority:  S

9. LEGAL BASIS FOR SUBMISSION:  505 (b)(1)

10. PHARMACOL. CATEGORY:  Anti-Parkinson

11. DOSAGE FORM:  Tablet, Film-coated

12. STRENGTH/POTENCY:  20, and 40 mg

13. ROUTE OF ADMINISTRATION:  Oral
14. Rx/OTC DISPENSED:  \( \surd \) Rx  \( \surd \) OTC

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

- \( \_ \) SPOTS product – Form Completed
- \( \surd \) Not a SPOTS product

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

- Chemical Name: \((E)-8-(3,4\text{-Dimethoxystyryl})-1,3\text{-diethyl}-7\text{-methyl}-3,7\text{-dihydro-1H-purine-2,6-dione}\)
- Mol. Formula: \(C_{20}H_{24}N_{4}O_{4}\)
- Mol. Weight: 384.43
- CAS Registry: [155270-99-8]

![Chemical Structure Image]

17. RELATED/SUPPORTING DOCUMENTS:

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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:**

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<td>Istradefylline for adjunctive treatment of Parkinson’s Disease</td>
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<td>(b) (4)</td>
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### 18. STATUS:

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<td>Microbiology</td>
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I. Recommendations

A. Recommendation and Conclusion on Approvability

From a CMC perspective, this application is approved (AP). The sponsor demonstrated the capacity to manufacture the drug product with adequate quality and stability.

Comment for Action Letter
We recommend a 6 month drug substance retest and a 4 month drug product expiry for all strengths.

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

There are no CMC Phase 4 activity recommendations.

II. Summary of Chemistry Assessments

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

Istradefylline is a novel, selective, adenosine A2A receptor antagonist. Istradefylline forms light yellow-green, needle-shaped, non-hygroscopic crystals with a melting point of 192.9°C. The drug substance is insoluble in aqueous media, regardless of pH, and is freely soluble in chloroform. The pH of aqueous slurries of Istradefylline ranges from 5.6 to 5.8. The drug substance dissociation constant is 0.78 and the partition coefficient ranges between 3.5 – 3.6. Istradefylline has five known, distinct polymorphs –

The drug substance manufacturing process consists of

Kyowa characterized the drug substance and its impurity profile adequately. Comprehensive specifications ensure the identity, strength, purity, and quality of the drug substance. The analytical procedures are specific for their intended purposes, stability-indicating when necessary, and validated. The container closure system is compatible with the drug substance and ensures stable storage, as demonstrated by the drug substance stability results. The post-approval stability commitment and protocol are adequate. The proposed retest period for the drug substance is 6 months. However, Kyowa only provided 24 months of long-term primary stability data. The recommended drug substance retest period is 6 months, based on ICH Q1E.

Tablets are biconvex, peach colored, film coated tablets. The shape of each biconvex tablet distinguishes the tablet strength: the 20 mg tablets are pillow-shaped; and the 40 mg tablets are almond-shaped. The tablets also include 20 or 40” debossed on the other side, depending on the tablet strength. The formulation contains compendial excipients, with the exception of the film-coat. Istradefylline tablet manufacturing uses

Comprehensive specifications ensure the identity, strength, purity, and quality of the drug product. The analytical procedures are appropriate, stability-indicating when necessary, and validated. Kyowa proposes for each tablet strength. The intended commercial package is 90-count, square, 60 cc high density polyethylene (HDPE) plastic bottles with closure and an induction seal.

The container closures are compatible with the drug product and ensure adequate protection during storage, as evidenced by the drug product stability results. The supportive stability data show that istradefylline tablets remain stable for up to 36 months when stored at 25°C/60%RH, up to 12 months when stored at 30°C/65%RH and up to 6 months when stored at 40°C/75% RH. The primary stability data show that the tablets remain stable for up to 30
months at 30°C/65%RH and up to 6 months when stored at 40°C/75% RH. The post-approval stability commitment and protocol are adequate. Kyowa provided 30 months of long-term primary stability data. The proposed expiration date is [b] months when stored at USP controlled room temperature (25°C or 77°F) with excursions permitted in the range of 15-30°C (59-86°F). The recommended drug product expiry is [b] months, based on ICH Q1E.

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

Istradefylline is indicated as adjunctive therapy to levodopa/carbidopa Parkinson’s disease. One 20 mg tablet to be taken orally, once a day, with or without food. An increase to 40 mg once daily. The recommended dosage for patients with moderate hepatic impairment is a fixed dose of [b] mg/day.

Table 1 - Proposed Dosing Regimen

<table>
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<th>Strength</th>
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<td>20 mg</td>
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<tr>
<td>40 mg</td>
<td>40</td>
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</tbody>
</table>

The [b] 20, and 40 mg strength tablets contain [b] 20, and 40 mg of istradefylline, respectively. Kyowa supplies the 20 mg drug product as biconvex, pillow-shaped, peach-colored, film-coated tablets debossed with “20” on the other side. Kyowa supplies the 40 mg drug product as biconvex almond-shaped, peach-colored, film-coated tablets debossed with “40” on the other side. The intended commercial packaging is 90-count HDPE bottles with closures. The recommended storage condition is 25°C with excursion permitted in the range of 15-30°C.

C. Basis for Approvability or Not-Approval Recommendation

From a CMC perspective, this application is approved. The sponsor identified CQA and established controls to ensure the quality of the drug substance and drug product. The batch analysis results confirm adequate drug substance and drug product quality at release. The data demonstrated adequate drug substance and drug product stability and support the recommended expiration dates. The intended commercial packaging presentations provide adequate protection of the drug product and ensure drug product quality over the proposed shelf-life. From a CMC perspective, the labeling is adequate.

III. Administrative

A. Reviewer’s Signature

Wendy I. Wilson

B. Endorsement Block

WWilson: 04-FEB-2008
MHeimann: 04-FEB-2008
RSood: 04-FEB-2008

C. CC Block

SGoldie
BFraser
NDA 22-075
**Evaluation:** The drug product labels include the necessary information on drug product identity, storage, and manufacturers. However, the labels lack the description of the dosage form. The sponsor should add “tablets” after the established name. For each tablet strengths, the example table on the label mimics the shape of the tablet and shows the corresponding strength debossing. The sponsor did not provide At the time of the original submission, Kyowa did not know the drug product tradename. The tentative tradename is The full prescribing information (PI) includes the pertinent chemistry, manufacturing, and controls information on dosage forms, strengths, description, inactive ingredients, how supplied, recommend storage conditions, and manufacturers. The PI also includes general properties information for the drug substance. As with the drug product label, the sponsor should provide updated labeling that includes the drug product tradename, 

*Information request (14-DEC-2007) – Provide revised drug product labels, adding “Tablets” after the established name to indicate the dosage form. Provide* 

*Kyowa Response:* 
We agree to add “Tablets” after the established name to indicate the dosage form. We intend to provide the revised label as a part of the labeling negotiations. We do not intend to prepare 

**Evaluation:** Adequate.

**B. Environmental Assessment Or Claim Of Categorical Exclusion**

In accordance with 21 CFR 25.31(b), Kyowa Pharmaceutical, Inc. claims a categorical exclusion from the environmental assessment requirements of 21 CFR 25.20(l) for the approval of the istradefylline tablets new drug application on the basis that the estimated concentration of istradefylline at the point of entry into the aquatic environment will be below 1 part per billion. Additionally, to the knowledge of Kyowa Pharmaceutical, Inc., no extraordinary circumstances exist that would warrant the preparation of an environmental assessment.

**Evaluation:** Adequate – This section meets the requirements under 21 CFR 25.31 (b) and 25.15 (d).

**C. Establishment Inspection**

Table 59 includes the facilities information submitted on 11-MAY-2007.
**Table 59 - Establishment Inspection Facilities**

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<td>Kyowa Hakko Kogyo Co., Ltd. Sakai Plant 1-1-5 Takamazu-chou, Sakai-ku Sakai-ku, Osaka, 590-8554 Japan Registration No. 30028075427 Contact Person: Mr. Nobuyuki Kato Director, International Development Coordination Kyowa Pharmaceutical, Inc. Princeton, NJ 08540 Telephone: 609-919-1100</td>
<td>Manufacturing, testing, and stability testing of the commercial drug substance</td>
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**III. List of Deficiencies to Be Communicated**

None.
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Wendy I. Wilson
2/4/2008 03:20:48 PM
CHEMIST

Ramesh Sood
2/4/2008 03:25:15 PM
CHEMIST