APPLICATION NUMBER:
22-257s000
21-304s007

CHEMISTRY REVIEW(S)
NDA 22-257

VALCYTE®
(valganciclovir hydrochloride)
Powder for Oral Solution
50 mg/mL

Roche Palo Alto LLC
Nutley, NJ

Division of Antiviral Drug Products
HFD-530
FDA CDER

Ted Chang, Ph.D.
ONDQA Pre-Marketing Assessment and
Manufacturing Science Division III/Branch VI
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<td>List of Deficiencies to be Communicated</td>
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CMC Review Data Sheet

1. **NDA 22-257**

2. **REVIEW #:** 1

3. **REVIEW DATE:** 26-AUG-2008

4. **REVIEWER:** Ted Chang, Ph.D.

5. **PREVIOUS DOCUMENTS:**

<table>
<thead>
<tr>
<th>Previous Documents</th>
<th>Document Date</th>
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<tbody>
<tr>
<td>Pre-NDA Meeting Response</td>
<td>03-SEP-2007</td>
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</tbody>
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6. **SUBMISSION(S) BEING REVIEWED:**

<table>
<thead>
<tr>
<th>Submission(s) Reviewed</th>
<th>Document Date</th>
<th>Subject Title</th>
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<tbody>
<tr>
<td>NDA 22-257</td>
<td>30-APR-2008</td>
<td>Original submission</td>
</tr>
<tr>
<td>NDA Amendment (N000-BC)</td>
<td>28-MAY-2008</td>
<td>Establishment Information and Cross References</td>
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7. **NAME & ADDRESS OF APPLICANT:**

<table>
<thead>
<tr>
<th>Name</th>
<th>Roche Palo Alto LLC</th>
</tr>
</thead>
</table>
| Address     | c/o Hoffmann-La Roche Inc.  
340 Kingsland Street  
Nutley, NJ 07110 |
| Representative | Wendy L. Corbett, Ph.D. |

8. **DRUG PRODUCT NAME/CODE/TYPE:**

<table>
<thead>
<tr>
<th>Proprietary Name</th>
<th>VALCYTE® Powder for Oral Solution</th>
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<tbody>
<tr>
<td>Non-Proprietary Name (USAN)</td>
<td>Valganciclovir Hydrochloride, Ganciclovir Valinate Hydrochloride</td>
</tr>
<tr>
<td>Code Names</td>
<td>Ro 107-9070/F01</td>
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<td>Chemistry Type</td>
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<tr>
<td>Submission Priority</td>
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9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: Anti-viral

11. DOSAGE FORM: Powder for Oral Solution

12. STRENGTH/POTENCY: 50 mg/mL (Re-Constituted solution)

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: __X__ Rx _____ OTC

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

_____ SPOTS product

__X__ Not a SPOTS product

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

Chemical Names: L-Valine, 2-[(amino-1,6-dihydro-6-oxo-9H-purin-9-yl)methoxy]-3-hydroxypropyl ester, monohydrochloride

9-[[2-Hydroxy-1-(hydroxymethyl)ethoxy]methyl]-guanine monoester with L-valine, monohydrochloride

US Adopted Name (USAN): VALCYTE® (valganciclovir hydrochloride)
International Non-proprietary Name (INN): valganciclovir
Laboratory Codes: RO1079070, Ro107-9070
Chemical Formula: $\text{C}_{14}\text{H}_{22}\text{N}_{6}\text{O}_{5} \cdot \text{HCl}$
Molecular Weight: 390.82
CAS Number: 175865-59-5 (for valganciclovir hydrochloride)  
175865-60-8 (for valganciclovir free base)

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

<table>
<thead>
<tr>
<th>DMF #</th>
<th>TYPE</th>
<th>HOLDER</th>
<th>ITEM REFERENCED</th>
<th>CODE¹</th>
<th>STATUS²</th>
<th>DATE REVIEW COMPLETED</th>
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<td>Review not required per policy</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)
Chemistry Review Data Sheet

B. Other Documents:

<table>
<thead>
<tr>
<th>DOCUMENT</th>
<th>APPLICATION NUMBER</th>
<th>DESCRIPTION</th>
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<tbody>
<tr>
<td>CMC Review #1</td>
<td>NDA 21-304</td>
<td>Tablets—Valganciclovir HCl 450-mg</td>
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18. STATUS:

<table>
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<tr>
<th>CONSULTS &amp; CMC RELATED REVIEWS</th>
<th>RECOMMENDATION</th>
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<th>STATUS/REVIEWER</th>
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<td>EES</td>
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<td>16-SEP-08</td>
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<td>LNC</td>
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<tr>
<td>Methods Validation</td>
<td>To be initiated post-approval</td>
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<tr>
<td>OSE DMETS</td>
<td>VALCYTE®, ACCEPTABLE</td>
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<tr>
<td>EA</td>
<td>Category exclusion granted</td>
<td>15-AUG-2008</td>
<td>Ted Chang</td>
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<tr>
<td>Microbiology</td>
<td>ACCEPTABLE</td>
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<td>Nilambar Biswal</td>
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</table>
The CMC Review for NDA 22-257

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product. Therefore this NDA is recommended for APPROVAL pending the “Acceptable” overall recommendation from Office of Compliance for all the facilities involved. As of 15-SEP-2008 this recommendation is still pending.

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

There are no Phase 4 commitments.

II. Summary of CMC Assessments

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

Valganciclovir hydrochloride is a pro-drug of the active pharmaceutical ingredient ganciclovir and consists of the valine monoester of ganciclovir. It exhibits improved oral bioavailability over its parent compound ganciclovir. Valganciclovir hydrochloride is indicated for the treatment of cytomegalovirus (CMV) retinitis in immuno-compromised patients. It inhibits replication of herpes viruses in vitro and in vivo. The virustatic activity of ganciclovir is due to inhibition of viral DNA synthesis by competitive inhibition of incorporation of deoxyguanosine-triphosphate into DNA by viral DNA polymerase, and incorporation of ganciclovir triphosphate into viral DNA causing the termination of, or very limited, further viral DNA elongation.”

The drug product—VALCYTE® Powder for Oral Solution—is a new formulation for the drug substance valganciclovir hydrochloride. This new formulation provides stability attribute (for pre-constitution dry powder) and dosing flexibility (for reconstituted oral solution). VALCYTE® Powder for Oral Solution fills the gaps of two approved drugs: 450-mg tablets (NDA 21-304 VALCYTE) and CYTOVENE-IV (NDA 19-661 for ganciclovir sodium for injection).

DRUG SUBSTANCE Satisfactory
CHEMISTRY REVIEW

Executive Summary Section

This section of Summary of CMC Assessment for the Drug Substance is excerpted from NDA 21-304 CMC Review #1, for the completeness of CMC review for NDA 22-257.

Valganciclovir is the valine monoester of ganciclovir, and consists of two diastereomers. Both diastereomers have the (S)-configuration at the valine chiral center and an approximately equimolar mixture of (R) and (S) configuration at the C-2 of the gerceryl side chain of the ganciclovir moiety. In vivo, both diastereomers are readily converted to ganciclovir, which is achiral. Two additional diastereomers having the R-configuration at the valine chiral center exist as impurities.

The drug substance is a hydrochloride salt and is freely soluble in aqueous solution, particular at low pH. The material exists as a white crystalline powder. Valganciclovir hydrochloride may contain up to \( \text{[redacted]} \). It is reversibly hygroscopic and will either absorb or release moisture under ambient humidity conditions, depending on the water content of the compound and the relative humidity of the surrounding atmosphere.

The structure of valganciclovir hydrochloride was confirmed by a combination of infrared, ultraviolet, 1H-NMR, 14C-NMR, mass spectra and elemental analysis. The information provided adequately supports the proposed structure of drug substance.

The proposed specification of the drug substance includes appearance, identity (IR, UV, chloride), water, sulfated ash, heavy metals, residual solvents, organic impurities (identified, total and individual other identified impurities, total and individual other unidentified impurities and total of all impurities), diastereomer ratio, enantiomeric purity, assay and particle size. The methods and method validations are adequate to support the specifications.

Three early process development batches as well as ten pilot-scale batches and three full-scale batches (the registration batches) of the commercial manufacturing process were produced. The early process development batches were manufactured at the research site, and pilot-scale batches and full-scale batches were manufactured at the Roche Colorado Corporation site. The batch analyses data comply with the proposed specifications.
Stress stability studies of the drug substance demonstrated that the material exhibits a good stability profile when exposed to extremes of heat, light, and humidity for periods up to eight weeks. No significant change in either the enantiomeric purity or the diastereomer ratio of the samples was observed. There was a slight but measurable increase in the levels of Ro 102-1592/000 (ganciclovir) in response to the heat and light stresses, but not under the high humidity conditions. The greatest effects were observed with the combination of heat and humidity.

At the time of approval, 24 months of primary stability data are available on the pilot-scale lots at 25°C/60%RH. The completed accelerated studies (40°C/75%RH) show that minor degradation is observable, although the assay and organic impurities of the DS remains within specification limits. Long term stability studies (25°C/60%RH) have shown no time-dependent changes in the assay, purity profile, diastereomer ratio or the enantiomeric purity up to 24 months, other than to

Based on the available stability test data, a re-test period for the DS requested by the sponsor is justified.

**DRUG PRODUCT**  
*Satisfactory*

After reconstitution with 91-mL of purified water, the resulting solution for oral administration is 100-mL in volume and 50-mg/mL valganciclovir free base in target strength.

The quality of manufactured drug products are ensured through in-process controls and release testing against specifications.
A battery of stability studies, long-term and stress, were conducted for the dry powder (up to 36 months), reconstituted solution (up to 3 months), antimicrobial preservative (i.e. [b](4) user test (i.e. low level challenge tests), in-use solution, and leachables/extractables for the PIBA and plastic oral dispenser. Stability data are adequate to support the proposed shelf-life of 2 years for VALCYTE Powder stored at 25°C with excursion permitted to 15-30°C, and 49 days shelf-life for reconstituted solution stored at 5°C.

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

The drug product—VALCYTE Powder for Oral Solution—is packaged as dried powder/granulates (containing 5-gram drug substance) in a (b)(4) glass bottle. The powder is reconstituted with 91-mL purified water to make approximately 100-mL solution, and capped with a press-in bottle adaptor (PIBA). The strength of the solution is 50-gram/mL of valganciclovir free base. The appropriate amount of solution is withdrawn with a plastic syringe-like oral dispenser and administered directly into a patient’s mouth. The PIBA and two oral dispensers are co-packaged with VALCYTE Powder for Oral Solution.

C. Basis for Approvability or Not-Approval Recommendation

This NDA provided adequate information on the raw material controls, manufacturing process, specifications, and container/closure system. It also provided sufficient stability data to assure identity, strength, purity and quality of the drug product during the shelf life. Labels have required information from the CMC perspective. Therefore this NDA is recommended for APPROVAL pending the “Acceptable” overall recommendation from Office of Compliance for all the facilities involved.

III. Administrative

A. Reviewer’s Signature

/s/ H. Ted Chang, Ph.D.

/s/ Norman R. Schmuff, Ph.D.
B. Endorsement Block

CMC Reviewer: H. Ted Chang, Ph.D.
Pharmaceutical Assessment Lead: Stephen P. Miller, Ph.D.
Branch Chief: Norman R. Schmuff, Ph.D.
Project Manager: David Araojo

C. CC Block

Orig. NDA 22-257
HFD-530/Division File
Filename: Review-NDA 22257 Roche Valcyte Powder CMC#1.doc

55 pages have been withheld immediately after this page as B4 (CCI/TS).
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Ted Chang
9/18/2008 11:27:55 AM
CHEMIST

Norman Schmuff
9/18/2008 08:43:46 PM
CHEMIST
The Executive Summary

A. Recommendation and Conclusion on Approvability

This NDA has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product. The Office of Compliance has provided—on October 16, 2008—an overall recommendation of “ACCEPTABLE” for all the manufacturing and testing sites. Therefore this NDA is recommended for APPROVAL from the CMC perspective.
### Establishment Evaluation Request

**Establishment:**
- CNF: 9590045
- FEI: 2000264888
- PATHRON INC. TORONTO REGION OPERATIONS
- 2100 SYNTEX COURT
- MISSISSAUGA, ONTARIO, CA

**DNF No:** AADA

**Responsibilities:** FINISHED DOSAGE MANUFACTURER

**Profile:** FOX

**OAI Status:** NONE

**Last Milestone:** OC RECOMMENDATION

**Milestone Date:** 16-OCT-08

**Decision:** ACCEPTABLE

**Reason:** DISTRICT RECOMMENDATION

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**Establishment:**
- CNF: 9516948
- FEI: 2002861690
- PATHRON INC. - BURLINGTON CENTURY OPERATIONS
- 977 CENTURY DRIVE
- BURLINGTON, ONTARIO, CA

**DNF No:** AADA

**Responsibilities:** FINISHED DOSAGE RELEASE TESTER

**Profile:** CTL

**OAI Status:** NONE

**Last Milestone:** OC RECOMMENDATION

**Milestone Date:** 12-JUN-08

**Decision:** ACCEPTABLE

**Reason:** BASED ON PROFILE

---

**Establishment:**
- CNF: 1710165
- FEI: 1710165
- ROCHE COLORADO CORP.
- 2075 NORTH 55TH ST
- BOULDER, CO 80301

**DNF No:** AADA

**Responsibilities:** DRUG SUBSTANCE MANUFACTURER

---

**Profile:** CSN

**OAI Status:** NONE

**Last Milestone:** OC RECOMMENDATION

**Milestone Date:** 20-JUN-08

**Decision:** ACCEPTABLE

**Reason:** DISTRICT RECOMMENDATION
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

---------------------
Ted Chang
10/17/2008 03:01:36 PM
CHEMIST

Norman Schmuff
10/20/2008 01:34:02 PM
CHEMIST