

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**22-257s000**

**21-304s007**

**OTHER REVIEW(S)**

**Division of Antiviral Drug Products**  
**REGULATORY PROJECT MANAGER REVIEW**

**Application Number:** 22-257/ Original-1  
21-304 (S-07)

**Name of Drugs:** VALCYTE (Valganciclovir) Powder for Oral Solution  
VALCYTE (Valganciclovir) Tablet

**Applicant:** Roche Palo Alto LLC

**Material Reviewed:**

**Submission Date(s):** April 30, 2008  
June 26, 2009

**Receipt Date(s):** May 1, 2008  
June 29, 2009

**BACKGROUND AND SUMMARY**

New Drug Application to support a new dosage form for VALCYTE, Powder for Oral Solution 50mg/mL, for the prevention of cytomegalovirus (CMV) disease in pediatric solid organ transplant recipients 4 months to 16 years of age at risk for developing CMV disease, (b) (4)  
(b) (4)

**REVIEW**

The following changes were agreed upon as follows:

1. INDICATIONS AND USAGE - This section was changed to add information on the use of Valcyte for CMV prophylaxis in children. The 'Pediatric Patients' subsection reads as follows.

Pediatric Patients

Prevention of CMV disease: (b) (4)

2. DOSAGE AND ADMINISTRATION - This section was changed to add information on the use of Valcyte in pediatric solid organ transplant recipients and to provide information on the preparation of Valcyte for oral solution. The Pediatric Patients subsection reads as follows:

## 2.3 Pediatric Patients

Prevention of CMV Disease: For pediatric patients 4 months to 16 years of age who have received a kidney or heart transplant, the recommended once daily dose of Valcyte starting within 10 days of transplantation until 100 days post-transplantation is based on body surface area (BSA) and creatinine clearance (CrCl) derived from a modified Schwartz formula, and is calculated using the equation below:

Pediatric Dose (mg) = 7 x BSA x CrCl (calculated using a modified Schwartz formula), where

$$\text{Mosteller BSA (m}^2\text{)} = \sqrt{\frac{\text{Height (cm)} \times \text{Weight (kg)}}{3600}}$$

$$\text{Schwartz Creatinine Clearance (mL / min / 1.73m}^2\text{)} = \frac{k \times \text{Height (cm)}}{\text{Serum Creatinine (mg / dL)}}$$

where k =

0.45 for patients aged < 1 year,

0.45 for patients aged 1 to < 2 years (note k value is 0.45 instead of the typical value of 0.55),

0.55 for boys aged 2 to < 13 years and girls aged 2 to 16 years, and

0.7 for boys aged 13 to 16 years.

All calculated doses should be rounded to the nearest 25 mg increment for the actual deliverable dose. If the calculated dose exceeds 900 mg, a maximum dose of 900 mg should be administered. Valcyte for oral solution is the preferred formulation since it provides the ability to administer a dose calculated according to the formula above; however, Valcyte tablets may be used if the calculated doses are within 10% of available tablet strength (450 mg). For example, if the calculated dose is between 405 mg and 495 mg, one 450 mg tablet may be taken.

## 2.4 Preparation of Valcyte for Oral Solution

Prior to dispensing to the patient, Valcyte for oral solution must be prepared by the pharmacist as follows [*see How Supplied/Storage and Handling (16)*]:

- Measure 91 mL of purified water in a graduated cylinder.
- Shake the Valcyte bottle to loosen the powder. Remove the child resistant bottle cap and add approximately half the total amount of water for constitution to the bottle and shake the closed bottle well for about 1 minute. Add the remainder of water and shake the closed bottle well for about 1 minute. This prepared solution contains 50 mg of valganciclovir free base per 1 mL.
- Remove the child resistant bottle cap and push the bottle adapter into the neck of the bottle.
- Close bottle with child resistant bottle cap tightly. This will assure the proper seating of the bottle adapter in the bottle and child resistant status of the cap.

- Store constituted oral solution under refrigeration at 2°C to 8°C (36°F to 46°F) for no longer than 49 days. Do not freeze.
- Write the date of expiration of the constituted oral solution on the bottle label.

The patient package insert, which includes the dosing instructions for patients and 2 oral dispensers, should be dispensed to the patient [*see Patient Counseling Information (17)*].

3. ADVERSE REACTIONS - The following information was added under the section of Clinical Trial Experience in Pediatric Patients subsection.

## 6.2 Clinical Trial Experience in Pediatric Patients

Valcyte for oral solution and tablets have been studied in 109 pediatric solid organ transplant patients who were at risk for developing CMV disease (aged 4 months to 16 years) and in 24 neonates with symptomatic congenital CMV disease (aged 8 to 34 days), with duration of ganciclovir exposure ranging from 2 to 100 days. The overall safety profile was similar in pediatric patients as compared to adult patients. However, the rates of certain adverse events and laboratory abnormalities, such as upper respiratory tract infection, pyrexia, nasopharyngitis, anemia, and neutropenia, were reported more frequently in pediatric patients than in adults [*see Use in Specific Populations (8.4), Clinical Studies (14.2)*].

4. USE IN SPECIFIC POPULATIONS - The following was added under the subsection of Pediatric Use.

## 8.4 Pediatric Use

Valcyte for oral solution and tablets are indicated for the prevention of CMV disease in kidney and heart transplant pediatric patients 4 months to 16 years of age at risk for developing CMV disease [*see Indications and Usage (1.2), Dosage and Administration (2.3)*].

The use of Valcyte for oral solution and tablets for the prevention of CMV disease in pediatric patients 4 months to 16 years of age with kidney or heart transplant is based on pharmacokinetic, safety, and efficacy data from an open-label trial with oral Valcyte (Valcyte for oral solution or tablets) in pediatric solid organ transplant recipients at risk for developing CMV disease. The results of this study were supported by previous demonstration of efficacy in adult patients [*see Adverse Reactions (6.2), Clinical Pharmacology (12.3), Clinical Studies (14.2)*].

The safety and efficacy of Valcyte for oral solution and tablets have not been established in children for:

- Prevention of CMV disease in liver transplant patients

- Prevention of CMV disease in solid organ transplants other than those indicated
- Prevention of CMV disease in pediatric solid organ transplant patients < 4 months of age
- Treatment of congenital CMV disease

The pharmacokinetic profile and safety of Valcyte for oral solution in children were studied in two open-label studies.

Study 1 was an open-label trial with oral Valcyte (Valcyte for oral solution or tablets) in pediatric solid organ transplant recipients at risk for developing CMV disease [see *Clinical Pharmacology* ([12.3](#)), *Clinical Studies* ([14.2](#))].

Study 2 was a pharmacokinetic and pharmacodynamic evaluation of Valcyte for oral solution in neonates with congenital CMV infection involving the central nervous system. Twenty-four neonates were enrolled in this study. All patients were treated for 6 weeks with a combination of intravenous ganciclovir 6 mg/kg twice daily and Valcyte for oral solution at doses ranging from 14 mg/kg to 20 mg/kg twice daily. The pharmacokinetic results showed that in infants > 7 days to 3 months of age, a dose of 16 mg/kg twice daily of Valcyte for oral solution provided ganciclovir systemic exposures (median  $AUC_{0-12h} = 23.6$  [range 16.8 – 35.5]  $\mu\text{g}\cdot\text{h}/\text{mL}$ ;  $n = 6$ ) comparable to those obtained in infants up to 3 months from a 6 mg/kg dose of intravenous ganciclovir twice daily ( $AUC_{0-12h} = 25.3$  [range 2.4 – 89.7]  $\mu\text{g}\cdot\text{h}/\text{mL}$ ;  $n = 18$ ) or to the ganciclovir systemic exposures obtained in adults from a 900 mg dose of Valcyte tablets twice daily.

The safety and efficacy of intravenous ganciclovir have not been established for the treatment of congenital CMV infection in infants and no similar disease occurs in adults; therefore, efficacy cannot be extrapolated from intravenous ganciclovir use in adults.

5. CLINICAL STUDIES - the following was added under the subsection of Pediatric Patients:

## 14.2 Pediatric Patients

Prevention of CMV in Pediatric Solid Organ Transplant Recipients: Sixty-three children, 4 months to 16 years of age, who had a solid organ transplant (kidney 33, liver 17, heart 12, and kidney/liver 1) and were at risk for developing CMV disease, were enrolled in an open-label, safety, and pharmacokinetic study of oral Valcyte (Valcyte for oral solution or tablets). Patients received Valcyte once daily as soon as possible after transplant until a maximum of 100 days post-transplant. The daily doses of Valcyte were calculated at each study visit based on body surface area and a modified creatinine clearance [see *Dosage and Administration* ([2.3](#))].

The pharmacokinetics of ganciclovir were similar across organ transplant types and age ranges. The mean daily ganciclovir exposures in pediatric patients were comparable to those observed in adult solid organ transplant patients receiving Valcyte 900 mg once daily [see *Clinical Pharmacology* ([12.3](#))]. No case of CMV disease was reported during the study. CMV viremia was reported in 7 (11%) patients during the study; however, none of these events fulfilled the definition of CMV syndrome. Based on the pharmacokinetic, safety, and

efficacy data from this study and extrapolated efficacy data from the adult study, oral Valcyte is indicated for the prevention of CMV disease in kidney and heart transplant children 4 months to 16 years of age at risk for developing CMV disease. Valcyte is not approved in adults for CMV prophylaxis in liver transplant patients; therefore, Valcyte is not recommended for CMV prophylaxis in pediatric liver transplant patients because efficacy cannot be extrapolated from adults.

Jaewon Hong, Pharm.D.  
Regulatory Project Manager  
Office of Antimicrobial Products  
Division of Antiviral Products

24 pages of Draft Labeling have been withheld immediately after this page as B4 (CCI/TS).

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

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NDA-22257

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ORIG-1

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ROCHE PALO  
ALTO LLC

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VALCYTE

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/s/  
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JAEWON HONG

11/16/2009

**MEMORANDUM**

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

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DATE: November 17, 2008

FROM: C.T. Viswanathan, Ph.D. *CV 11/17/08*  
Associate Director - Bioequivalence  
Division of Scientific Investigations (DSI)

TO: Debra Birnkrant, M.D.  
Director, Division of Antiviral Products (DAVP)

SUBJECT: Review of EIRs Covering NDA 22-257, Valcyte®  
(valganciclovir HCl) Powder for Oral Solution,  
50 mg/mL (Free Base), Sponsored by Roche Palo Alto LLC

At the request of DAVP, DSI audited the clinical and analytical portions of the following bioequivalence studies. This report is limited to the audit of analytical portions of the following studies at [REDACTED] (b)(4). The audits of the clinical portions of the studies were covered in DSI's report to DVAP dated 10/24/08.

**Study WP 16302:** "A bioequivalence study comparing ganciclovir from the valganciclovir oral solution and the commercial valganciclovir 450 mg tablet (Valcyte®) at a dose of 900 mg in kidney transplant recipients"

**Study WV 16726:** "Safety and pharmacokinetics of valganciclovir syrup formulation in pediatric solid organ transplant recipients"

**Study CASG 109:** "A Phase I/II Pharmacokinetic and Pharmacodynamic Evaluation of Oral Valganciclovir in Neonates with Symptomatic Congenital Cytomegalovirus (CMV) Infection"

Following the inspection at [REDACTED] (b)(4) [REDACTED] (b)(4) (11/3-7/08), Form 483 was issued.

As stated in DSI's 10/24/08 report, the analytical reports for the studies did not indicate problems with the assay. However, audit of the source data at analytical site revealed significant problems with chromatographic integration that could not be discerned from the analytical reports submitted in the NDA for

the above studies. Evaluation of the significant bioanalytical audit findings follows:

**Studies WP16302, WP16726 and CASG109:**

**I. Inconsistency in integration of chromatograms.**

**a. Failure to properly integrate several chromatograms.**

**Manual integrations were carried out by modifying parameters from the autointegration.**

The firm automatically integrated chromatograms and modified the integration (i.e. manual integration) of selective chromatograms. The inspection found that the parameters used for automatic integration failed to produce consistent integration in that automatic integrations of similar analyte peaks were inconsistent between chromatograms. Similarly, selection of chromatograms for manual integration was not consistent and modification cannot be justified.

In almost all of the chromatograms, the integration parameters chosen to integrate the peak area and the resulting plasma drug concentrations results were not accurate, and possibly overestimated (Exhibit 1). This is because a significant portion of tailing was included, often inconsistently, in integrating chromatographic peaks.

**b. Failure to reject analytical runs in that QCs at a given level were modified by manual integration and brought to acceptance. Several QC chromatograms were modified by manual integration.**

The inspection found that several quality control (QC) chromatograms (b)(4) were modified by manual integration without justification. Particularly, in the analytical runs identified in the table below, duplicate QCs at one or more concentrations or majority of QCs were modified without justification, possibly in an attempt to bring the runs into acceptance. Therefore, the acceptability of the analytical runs cannot be assured. For example, there was no justification for manual integration of both low QCs in analytical run gan060224 in Study WP16302 (Exhibits 2 and 3). With manual integration, one of the duplicate low QCs barely met QC acceptance (b)(4) of nominal) and the other failed. Failure of both QCs at a given concentration or failure of (b)(4) of total QCs would result in rejection of a run per the firm's procedures. It should be noted that a

majority of the modified QCs were from the runs listed below (b) (4)

**Table 1**

Study	Analytical run	QCs Modified
WP16302	GAN051206	Both QCL, QCH
	GAN060221	Both QCL
	gan060224	Both QCL, Both QCM
	gan060509	Both QCL, Both QCM, QCH
	Gan060419a*	QCL, QCM, QCH, QCHE
WP16726	GAN041216a	Both QCL, QCH
	GAN041224	Both QCL, Both QCM, QCH
	GAN050822	Both QCL, QCM
	GAN050901	QCL, Both QCM, Both QCH, QCVH
	GAN050909	QCL, QCM, QCH, Both QCHE
CASG109	GA040826	Both QCL
	GAN041013	Both QCL, Both QCH, QCHE
	GAN041102	Both QCL, QCH, QCHE, QCHV
	GAN041224	Both QCL, Both QCM, QCH, Both QCHV
	gan050808	QCL, Both QCM, Both QCH, Both QCHE, QCVH
	GA040830*	QCL, QCM, QCHEdil
	Gan050630*	QCL, QCM, QCH, QCHE

During the inspection, the firm concurred with the objectionable findings and agreed to correct their integration procedure.

**II. Storage stability cannot be assured.**

Studies WP16302 and WP16726 were conducted for a period of 1 year, and the study samples were analyzed between 6 months (WP16302) and 1 year (WP16726). Study CASG109 was conducted over a 4½ year period and samples were analyzed for 1½ years. The firm had frozen stability data for only 3 months. It is not known if this stability period covers the storage period (b) (4) of the pharmacokinetic (PK) samples for the above studies. This could not be discerned during the inspection as there was no documentation of sample collection dates at (b) (4). Further, (b) (4) did not receive the PK samples directly from the clinical sites, instead the sponsor collected the samples from the clinical sites and shipped them to (b) (4) in installments.

**Conclusions:**

Based on the findings from the analytical inspection, the concentration data for Studies WP16302, WP16726 and CASG109 are not accurate and not acceptable as submitted in the NDA.

To assure the accuracy of analytical runs and the resulting drug concentrations, the firm needs to identify a set of integration parameters and integrate all chromatograms within a run in a consistent manner for all runs. The resulting concentrations from acceptable analytical runs can be used for pharmacokinetic and/or pharmacodynamic evaluations for Studies WP16302, WP16726 and CASG109, following demonstration of long-term stability. The sponsor should provide storage durations of the PK samples for the studies, and provide long-term frozen stability data to cover the storage periods.

The above conclusions should be evaluated along with the conclusions reported in DSI's report dated 10/24/08.

After you have reviewed this transmittal memo, please append it to the original NDA submission.

**Final Classification:**

**VAI:**

(b) (4)

cc:

HFD-45/Vaccari/RF

HFD-48/Subramaniam/CF

DAVP/Araojo/NDA 22-257

OTS/OPS/DCP4/Arya/Reynolds

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/s/

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Sriram Subramaniam  
11/18/2008 08:53:20 AM  
PHARMACOLOGIST  
Sent on behalf of Dr. Viswanathan.

**MEMORANDUM**

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

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DATE: October 22, 2008

FROM: Sriram Subramaniam, Ph.D.  
Jacqueline A. O'Shaughnessy, Ph.D.  
Division of Scientific Investigations

THROUGH: C.T. Viswanathan, Ph.D. *martin K. Jan 10/24/08*  
Associate Director - Bioequivalence  
Division of Scientific Investigations (DSI)

TO: Debra Birnkrant, M.D.  
Director, Division of Antiviral Products (DAVP)

SUBJECT: Review of EIRs Covering NDA 22-257, Valcyte®  
(valganciclovir HCl) Powder for Oral Solution,  
50 mg/mL (Free Base), Sponsored by Roche Palo Alto LLC

At the request of DAVP, DSI audited the clinical and analytical portions of the following bioequivalence studies.

**Study WP 16302:** "A bioequivalence study comparing ganciclovir from the valganciclovir oral solution and the commercial valganciclovir 450 mg tablet (Valcyte®) at a dose of 900 mg in kidney transplant recipients"

**Study WV 16726:** "Safety and pharmacokinetics of valganciclovir syrup formulation in pediatric solid organ transplant recipients"

**Study CASG 109:** "Safety and pharmacokinetics of valganciclovir syrup formulation in pediatric solid organ transplant recipients"

The above studies were multicenter studies. Per DAVP's request, the following clinical sites were audited:

Study WP 16302: Indiana University Medical Center, Surgery and Microbiology/Immunology, Indianapolis, IN

Study WV 16726: UCLA Center for Health Sciences, Division of Pediatric Nephrology, Los Angeles, CA

Study CASG 109: University of Texas Southwestern Medical Center,  
Department of Pediatrics, Dallas, TX.

The analytical portions of the above studies were conducted at

(b) (4)

Following the inspections at the Indiana University Medical Center, Indianapolis, IN (7/29-31/08), UCLA Center for Health Sciences, Los Angeles, CA (10/16-21/08), and University of Texas Southwestern Medical Center, Dallas, TX (7/29-31/08), Form 483s were issued.

The evaluation of the inspectional findings from the clinical sites follows. Only clinical findings specific to the pharmacokinetic (PK) portion of the studies are part of this report. Review of inspectional findings related to the safety and efficacy components of Studies WV 16726 and CAG 109 were forwarded separately by DSI's Good Clinical Practice Branch I.

Study WP 16302: Indiana University Medical Center, Surgery &  
(n=9) Microbiology/Immunology, Indianapolis, IN.

1. **Samples of the test drugs were not retained at the clinical site. On 4/26/06 all intact bottles of study drugs were collected by study monitor.**

The clinical site did not retain reserve samples for the bioequivalence study as required by 21 CFR 320.38. Also, the unused drugs were returned to the sponsor. The clinic stated that the sponsor's protocol did not require reserve sample retention, and the unused drugs were returned per protocol. Nonetheless, due to the lack of reserve samples, the authenticity of the test and reference drugs used in the bioequivalence study cannot be confirmed.

2. **On 8/27/05 PK blood samples for Subject #103 were not always drawn at Protocol specified intervals. The subject was dosed at 10:35.**

The 2, 3, 4, 6 and 8 hour PK sample collections for Subject 103 deviated by 20 minutes. Nonetheless, review of PK data sets in EDR indicates that the observed PK sampling times were reported.

Study WV 16726: UCLA Center for Health Sciences,  
(n=5) Division of Pediatric Nephrology, Los Angeles, CA

3. **The following pharmacokinetic (PK) assessments were not collected according to the protocol. Specifically, protocol WV 16726 section 5.2.4 titled Pharmacokinetic Assessment (and Appendix 5) required samples to be collected on Day 7-**

**Day 14, Week 6 , Week 10 and Day 100. Samples for Week 6, Week 10 and Day 100 were to be collected anytime post dose or at the time of the blood draw for safety assessments.**

Subject #	PK Time	Dosing Time	Observed PK Sample time
8601	Week 6	13:30	11:21
	Week 10	14:00	09:30
	Day 100	13:30	10:02
8602	Week 6		Not done
	Week 10	11:00	08:59
	Day 100		Not done
8603	Week 6	10:30	07:00
	Week 10	12:00	08:00
	Day 100		Not done
8604	Week 6		Not done
	Week 10		Not done
8605	Week 6		Not done
	Week 10	08:30	06:40

As indicated in the table, PK samples were either not collected or collected prior to dosing. Section 5.2.4 of the protocol states PK sampling for Weeks 6 and 10, and Day 100 "can be taken at any time after vanganciclovir administration". Nonetheless, review of PK data sets in EDR indicates that the observed PK sampling times were reported at Weeks 6 and 10, and Day 100.

#### **4. Discrepancies in dosing.**

The available source records do not demonstrate the daily doses administered to subjects when they were not hospitalized. The drug dispensing records only indicate the drugs that were dispensed to and returned by the subjects. Also, it is not known whether the entries were contemporaneous as there were no dates and initials of the persons who entered the data, and often the return dates were not known. Since only drug dispensation and return information are available, daily doses can only be estimated for the non hospitalization period assuming the drugs were administered per protocol with no dosing discrepancies. Therefore, the exact daily doses for the non hospitalization periods cannot be confirmed for the five study subjects enrolled at this site.

**Study CASG 109: University of Texas Southwestern Med. Ctr.,**  
(n=9) **Department of Pediatrics, Dallas, TX.**

#### **5. Investigation was not conducted in accordance with the investigational plan in that Subject 64 was misdosed.**

According to the home dosing administration diary, subject 0064 received 18.4 mg of ganciclovir for doses 5-12 (May 22-25, 2005) instead of 18 mg, as instructed by Dr. Sanchez. Furthermore, doses 13-26 (May 26-June 1, 2005) were not administered because

the IV line was out and not re-inserted. Because subject 0064 vomited after the oral valganciclovir dose on June 5, 2005, the parent re-dosed the subject, against the written instructions provided to the parent. The OCP reviewer should consider the impact of misdosing on PK assessments for subject 0064.

**Analytical Site:**

(b) (4)

Due to competing priorities, the inspection of Analytico B.V. has been scheduled during October 31, 2008 onwards, following the user fee goal date. In the meantime, to facilitate the approval process, DSI conducted a preliminary review of the bioanalytical reports submitted for Studies WV 16302, WV 16726, and CASG 109. The assay results reported in the bioanalytical report do not reveal significant problems with the assay used by Analytico for estimation of ganciclovir. Should there be any change in DSI's conclusion of the analytical results following the inspection at Analytico B.V., DSI will provide the revised conclusion to DAVP.

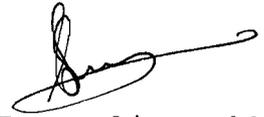
**Conclusions:**

Based on the findings from the clinical inspections:

- The authenticity of the test and reference products used in the bioequivalence Study WP 16302 cannot be assured as the clinical site failed to retain reserve samples (Item 1).
- The OCP reviewer should consider the impact of the dosing and PK sampling deviations (Items 3-5) on Studies WV 16726 and CASG 109.

After you have reviewed this transmittal memo, please append it to the original NDA submission.

  
Sriram Subramaniam, Ph.D.

  
for Jacqueline O'Shaughnessy, Ph.D.

**Final Classifications:**

**VAI: Indiana University Medical Center, Surgery &  
Microbiology/Immunology, Indianapolis, IN.**

(Reason for change in classification: The 483 finding for reserve retention was appropriate as the clinical site violated the reserve sample retention requirement. However, the fault also lies with the sponsor as the sponsor's protocol did not require reserve sample retention, and the protocol required returning unused samples).

**VAI: University of Texas Southwestern Med. Ctr., Department of  
Pediatrics, Dallas, TX.** (refer to GCPB I's review to DAVP dated 9/25/08 for the change in classification)

**VAI: UCLA Center for Health Sciences,  
Division of Pediatric Nephrology, Los Angeles, CA**

**CC:**

HFD-45/RF

HFD-45/Vaccari

HFD-48/Subramaniam/CF

DAVP/Araojo/NDA 22-257

OTS/OPS/DCP4/Arya/Reynolds

HFR-CE7545/Austin

HFR-SW1580/Stone

HFR-PA250/Van Leeuwen

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FACTS: (b) (4)

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/s/

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Sriram Subramaniam  
10/24/2008 01:18:52 PM  
PHARMACOLOGIST

# MEMORANDUM

**To:** David Araojo, PharmD  
Division of Antiviral Products

**From:** Iris Masucci, PharmD, BCPS  
Division of Drug Marketing, Advertising, and Communications  
for the Study Endpoints and Label Development (SEALD) Team, OND

**Date:** October 9, 2008

**Re:** Comments on draft labeling for Valcyte (valganciclovir HCl)  
NDA 22-257

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We have reviewed the proposed label for Valcyte (FDA version dated 9/30/08) and offer the following comments. These comments are based on Title 21 of the Code of Federal Regulations (201.56 and 201.57), the preamble to the Final Rule, labeling Guidances, and FDA recommendations to provide for labeling quality and consistency across review divisions. We recognize that final labeling decisions rest with the review division after a full review of the submitted data.

## GENERAL COMMENTS

- Please consider deleting all internal company study titles [REDACTED] (b) (4) from text and tables in the label. They can be confusing to the reader and should be included only if they are well established descriptors that are widely understood in the medical community.
- Throughout the text and tables in the label, we suggest using “intravenous ganciclovir” instead of “Cytovene-IV.” When other drugs are mentioned in a label, we generally use established names instead of trade names.
- There is some inconsistency in the instructions for preparing the oral solution. Section 2.1 says that it “should be done by a pharmacist,” section 2.4 says that it “must be done by a pharmacist,” and section 16 says “it is recommended that ... it be done by a pharmacist” (emphasis added). Can we be consistent in our recommendation?
- In some sections of the label (e.g., “10 Overdosage,” “12.3 Pharmacokinetics,” and “14 Clinical Studies”), there is some odd formatting when subheadings are used. The first sentence of the text under the subheading appears on the same line as the subheading title, followed by “...” Please review and revise as needed throughout.
- Please insert horizontal lines spanning the entire page between Highlights and Contents and between Contents and the Full Prescribing Information (FPI).

- We note that the FPI contains a mix of font styles (e.g., most text is Times New Roman, but underlined subheadings are Arial). Please consider using one font throughout to improve readability.

## HIGHLIGHTS

- We note that Highlights is considerably longer than ½ page. Please consider if a waiver should be granted for the ½ page requirement or if we should make an effort to pare it down to fit on ½ page.
- *“Valcyte® (valganciclovir hydrochloride) Tablets and Valcyte® (valganciclovir hydrochloride) Powder for oral solution”*

The “®” symbol should be removed from Highlights. If the sponsor wants to use it in the label, we ask that it appear upon first use of the trade name in the FPI and not again thereafter.

Please change “Tablets” and “Powder” to all lower case lettering because they are not part of the trade name.

- *“Initial U.S. Approval: 2001”*

Please insert a hard return (white space) after this line.

- Please correct the formatting of the indenting of bullets throughout Highlights.

## Boxed Warning

- *“WARNING: HEMATOLOGIC TOXICITY, CARCINOGENICITY AND TERATOGENICITY”*

We note that the risk of aspermatogenesis does not seem to be captured in the boxed warning “title.” We suggest revising the title to:

WARNING: HEMATOLOGIC TOXICITY, CARCINOGENICITY,  
TERATOGENICITY, and IMPAIRMENT OF FERTILITY

or

WARNING: HEMATOLOGIC TOXICITY and CARCINOGENICITY/  
TERATOGENICITY/ IMPAIRMENT OF FERTILITY

Any changes made to the warning title must also be made in Contents and the FPI.

- Please correct the indenting of the bulleted text in the boxed warning.
- *“Clinical toxicity of Valcyte which is metabolized to ganciclovir includes granulocytopenia, anemia, and thrombocytopenia”*

We suggest adding commas before and after the phrase “which is metabolized to ganciclovir.”

- *“In animal studies ganciclovir was carcinogenic, teratogenic, and caused aspermatogenesis (5.2, 5.3)”*

Please insert a comma after “In animal studies.”

Please add 5.4 to the cross-reference for carcinogenicity.

## **Recent Major Changes**

- The text in this section should be neither bolded nor underlined.

## **Indications and Usage**

- *“Valcyte is a nucleoside analogue CMV DNA polymerase inhibitor indicated for:”*

Because this is the first use of the acronym “CMV” in the label, we suggest it be defined here instead of on the subsequent line.

- For the three underlined “titles” in this section, we suggest that the cross-reference in parentheses not be underlined for ease of reading.

- *“The safety and efficacy of Valcyte have not been established for:”*

Please have this sentence begin a new line under “Limitations of Use.”

- *“The prevention of CMV disease in liver transplant patients  
The prevention of CMV disease in other solid organ transplant patients such as lung  
transplant patients”*

When reading the list of limitations, one could infer that “other solid organ transplants” means those other than liver transplant because the liver transplant bullet immediately precedes it. Please consider clarifying. We suggest that the second bullet read, “The prevention of CMV disease in solid organ transplants other than those indicated” or something similar.

## **Dosage and Administration**

- Please change the cross-references in the table headings for adults and pediatric patients to 2.2 and 2.3.

- *“Dosage according to dosage algorithm (2.6)”*

We recommend changing the first “Dosage” to “Dose” to make the statement a command. In addition, the cross-reference at the end of the line should be deleted because there is one above it to the pediatric dosing section (2.3).

- Please consider if the bullets about the need to reconstitute the powder and avoiding overdosage are truly relevant for Highlights. We suggest deletion.
- For the last bullet about renal impairment, we suggest it begin, “Adults with Renal Impairment” for accuracy.

### **Dosage Forms and Strengths**

- We suggest using lower case lettering for “oral solution.”

### **Warnings and Precautions**

- *“Do not administer Valcyte if the absolute neutrophil count is <500 cells/uL, the platelet count is <25,000/uL, or the hemoglobin is < 8 g/dL.”*

Please delete the three uses of “the” in this sentence for conciseness. Also, please change the semi-colon before this sentence to a period.

- In the third bullet about teratogenesis/mutagenesis, we suggest that the cross-reference be only to section 5.3 for ease of reading. Section 5.3 in the FPI will then direct the reader to the other sections of the label.

### **Adverse Reactions**

- We suggest revising this section slightly to make it clearer that the two lists are for adults vs. pediatric patients. We recommend:
  - Adults: Most common adverse reactions (reported in at least one indication by > 25% of patients) are diarrhea, nausea, tremor, graft rejection, neutropenia, and anemia. (6.1)
  - Pediatric patients: Most common adverse reactions (reported in > 10% of patients) are diarrhea, pyrexia, hypertension, upper respiratory tract infection, vomiting, anemia, neutropenia, constipation, and nausea (6.2)

Please note that we have also made some editorial changes above.

### **Drug Interactions**

- Please correct formatting at the beginning of this section.
- *“Mycophenolate Mofetil (MMF): In patients with renal impairment may increase ganciclovir concentrations and levels of MMF metabolites. Monitor for ganciclovir and MMF toxicity (7)”*

We recommend using lower case letters for “mofetil” in this bullet.

## Revision Date

- The month and year must be filled in upon approval. The brackets around the date should be deleted.
- 

## CONTENTS

- If Highlights and Contents do not all fit on one page, we suggest that Contents begin on page 2 rather than splitting it between pages.
  - Once the FPI has been finalized, Contents must be updated to ensure accuracy of the numbering and section titles. Then, any corresponding changes should be made to the Highlights and cross-references throughout the label.
- 

## FULL PRESCRIBING INFORMATION

### Boxed Warning

- Please consider revising the warning “title” as mentioned under Highlights.
- For ease of reading, we suggest that the two sentences in the box be presented as either two separate paragraphs or two bullets. If they are separated, we suggest that the first sentence conclude with a cross-reference to 5.1, and second one to 5.2, 5.3, and 5.4.

### 1.3 Limitations of Use

- We prefer the presentation of the limitations of use that is in Highlights, which has four bullets under “The safety and efficacy of Valcyte has not been established for:”
- As under Highlights, please consider rewording “in other solid organ transplants” for clarity.

### 2.1 General Dosing Information

- *“Strict adherence to dosage recommendations is essential to avoid overdose.”*

What is the origin of this statement? The take-home message seems unclear. Wouldn't this hold true for nearly all prescription drugs?

### 2.2 Adult Patients

- We suggest deleting the bullets from the two subheadings in the section. Underlining the titles gives them adequate prominence.
- We recommend deleting the box from the induction and maintenance dose instructions for ease of reading. Using bullets here could be useful.

## 2.3 Pediatric Patients

- *“For pediatric patients 4 months to 16 years of age who have received a kidney or heart transplant, the recommended once daily dose of Valcyte starting within 10 days of transplantation until 100 days post- transplantation is based on (BSA)...”*

Please spell out “body surface area” before the acronym is defined.

## 2.4 Preparation of Valcyte Oral Solution

- *“Write the date of expiration of the constituted oral solution on the bottle label.”*

We suggest that this line be moved to the bulleted list before “Store constituted oral solution under refrigeration...”

- *“The patient package insert which includes the dosing instructions for patients, and 2 oral dispensers should be dispensed to the patient.”*

Please add a cross-reference to section 17.2 to the end of this sentence.

## 2.5 Renal Impairment

- Table 1

We recommend changing the table title to “Dosage Recommendations for Adult Patients with Impaired Renal Function” to clarify that the table refers to adults only.

For ease of reading, we recommend using a smaller font for the creatinine clearance calculation section.

- After the calculation instructions, please consider if a line should be added to this section describing the lack of data in children with renal impairment.

-  (b) (4)

Again, we recommend saying “adult patients” instead of just “patients” for clarity.

## 2.6 Handling and Disposal

- *“There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.”*

We recommend moving this sentence to the end of the preceding paragraph rather than having it be a separate paragraph.

### 3 Dosage Forms and Strengths

- We recommend underlining “Valcyte tablets” and “Valcyte powder for oral solution” instead of using bullets.

#### 5.1 Hematologic effects

- Please capitalize “effects” in the section title.

#### 5.2 Impairment of Fertility

- *“Animal data indicate administration of ganciclovir causes inhibition of spermatogenesis and subsequent infertility.”*

Should “in males” be added to the end of this sentence for clarity?

- *“In humans, Valcyte at the recommended doses may cause temporary or permanent inhibition of spermatogenesis.”*

Again, should we say, “In human males”?

#### 5.3 Teratogenesis and Mutagenesis

- *“Because of the potential to cause birth defects women of childbearing potential should be advised to use effective contraception during treatment.”*

Please insert a comma after “defects.”

- Please add 13.3 to the cross-reference at the end of this section.

#### 5.4 Carcinogenesis

- Please correct the formatting at the beginning of this section
- *“Valcyte should., therefore considered as a potential carcinogen in humans.”*

Please revise to, “Valcyte should therefore be considered a potential carcinogen...”

### 6 Adverse Reactions

- Please add a second bullet for “Acute renal failure” at the beginning of this section.
- *“The most common adverse events and laboratory abnormalities reported in at least one indication by > 25% of adult patients treated with Valcyte are diarrhea, pyrexia, nausea, tremor, graft rejection, neutropenia, and anemia. The most common adverse events and laboratory abnormalities reported in > 10% of pediatric solid organ transplant recipients*

*treated with Valcyte at the recommended dose are diarrhea, pyrexia, hypertension, upper respiratory tract infection, vomiting, anemia, neutropenia, constipation, and nausea.”*

Would it be correct to change “adverse events” to “adverse reactions” in these two sentences?

## **6.1 Clinical Trial Experience in Adult Patients**

- *“Adverse events known to be associated with ganciclovir usage can therefore be expected to occur with Valcyte.”*

Please change “events” to “reactions” in this sentence.

- Please correct the formatting of the paragraph before Table 2 and the table title itself.
- Table 2

Should the title and text of this table say “adverse events” or “adverse reactions”?

## **6.2 Clinical Trial Experience in Pediatric Patients**

- *“Valcyte has been studied in 109 pediatric solid organ transplant patients who are at risk of developing CMV disease (aged 4 months to 16 years) and in 24 neonates with symptomatic congenital CMV disease (aged 8 to 34 days), with duration of ganciclovir exposure ranging from 2 to 100 days.”*

Please change “who are at risk” to “who were at risk.”

- We suggest deleting “Dosage and Administration” and “Clinical Pharmacology” from the cross-reference at the end of this section.

## **6.3 Postmarketing Experience**

- Please consider if simply referring the reader to the ganciclovir label is appropriate. The way this section is written implies that the trial data for the two drugs is similar and the postmarketing data for the two drugs is similar. Is that right? If there actually is postmarketing data for Valcyte, it should be included here. If not, please consider if this section is even needed in the label.

## **7 Drug Interactions**

- We recommend deleting the bullets from this section.
- *“Valcyte tablets or powder for oral solution should be taken with food [see Clinical Pharmacology (12.3)]”*

Should this sentence really be included under “Drug Interactions”? We generally do not include a recommendation to take with food in this section.

- *“Drug-drug interaction studies were conducted in patients with normal renal function.”*

We recommend revising to “... were conducted with ganciclovir in patients with...”

- *“Established and other potentially significant drug interactions conducted with ganciclovir are listed in Table 6.”*

We recommend moving this sentence to the end of the paragraph at the beginning of the section that begins with “No in vivo drug-drug interaction studies...”

## 8.1 Pregnancy

- Please delete the bolding from the text in this section.

## 8.4 Pediatric Use

- *“The results of this study were supported by previous demonstration of efficacy in adult patients [see Indications and Usage (1.2), Dosage and Administration (2.3), Adverse Reactions (6.2), Clinical Pharmacology (12.3), Clinical Studies (14.2)].”*

We recommend deleting “Indications and Usage” and “Dosage and Administration” from this cross-reference because they are unnecessary here.

- In the bulleted list of non-indicated uses, please consider revising “other solid organ transplants” as recommended above. Please also delete the underlining from the last two bullets.
- *“Study 1 was an open-label trial with oral Valcyte (Valcyte powder for oral solution or tablets) in pediatric solid organ transplant recipients at risk for developing CMV disease [see indications and Usage (1.2), Dosage and Administration (2.2), Adverse Reactions (6.x), Clinical Pharmacology (12.3), Clinical Studies (14.4)].”*

We recommend deleting “Indications and Usage,” “Dosage and Administration,” and “Adverse Reactions” from this cross-reference because they seem unnecessary.

- *“Study 2 was a pharmacokinetic and pharmacodynamic evaluation of valganciclovir powder for oral solution in neonates with congenital CMV infection involving the central nervous system.”*

Was the drug used in this study the marketed formulation? If so, we recommend changing “valganciclovir powder for oral solution” to “Valcyte.” We also recommend the same change in the last sentence of this paragraph.

## 8.6 Renal Impairment

- Please correct the formatting for this section and 8.7.

### 12.3 Pharmacokinetics

- We recommend deleting the bullets from the beginning of this section.
- *“Therefore, dosage adjustment is required for patients with impaired renal function.”*

Please add a cross-reference to 2.5 at the end of this sentence.

- We recommend that the “Pediatrics” subheading be changed to “Pharmacokinetics in Pediatric Patients” for consistency with the adult subsection. The same change should be made to the “Geriatrics” subsection that follows.
- *“In this study, patients received oral doses of valganciclovir to produce exposure equivalent to an adult 900 mg dose [see Dosage and Administration (2. 5), Adverse Reactions (6. 2), Use in Specific Populations (8.4), Clinical Studies (8.2)].”*

In this sentence under “Pediatrics,” please change the “Clinical Studies” cross-reference number to 14.2.

- Table 9

In the table footnote, please spell out “PK.” In addition, please change “affects” to “effects” for grammatical correctness.

- *“However, because valganciclovir is rapidly and extensively converted to ganciclovir, interactions associated with ganciclovir will be expected for Valcyte.”*

Please add a cross-reference to section 7 at the end of this sentence under “Drug Interactions” to point the reader to the clinical implications of these interactions.

### 13.3 Reproductive and Developmental Toxicity

- We suggest moving the “footnote” at the end earlier in the section so it does not get overlooked.

### 14.1 Adult Patients

- Please indent the subheading title “Maintenance Therapy of CMV Retinitis” for consistency with the other subheadings.

### 14.2 Pediatric Patients

- *“Dose (mg) = 7 x BSA x CrCl [see Dosage and Administration (2.2)]”*

Please move the cross-reference from the equation line to the preceding sentence introducing it.

- *“Based on the pharmacokinetic, safety, and efficacy data from this study and extrapolated efficacy data from the adult study, oral Valcyte is recommended for approval for the prevention of CMV disease in kidney and heart transplant children 4 months to 16 years of age who are at risk of developing CMV disease.”*

Please consider revising the phrase “Valcyte is recommended for approval” to either “is indicated for” or “is approved for.” The current wording sounds like it comes from an Agency review recommending approval.

## 15 References

- The list of references on safe handling/disposal is outdated. Per the Office of Oncology Drug Products, the correct references should be:
  - NIOSH Alert: Preventing occupational exposures to antineoplastic and other hazardous drugs in healthcare settings. 2004. U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, DHHS (NIOSH) Publication No. 2004-165.
  - OSHA Technical Manual, TED 1-0.15A, Section VI: Chapter 2. Controlling Occupational Exposure to Hazardous Drugs. OSHA, 1999. [http://www.osha.gov/dts/osta/otm/otm\\_vi/otm\\_vi\\_2.html](http://www.osha.gov/dts/osta/otm/otm_vi/otm_vi_2.html)
  - American Society of Health-System Pharmacists. ASHP guidelines on handling hazardous drugs. *Am J Health-Syst Pharm.* 2006; 63:1172-1193.
  - Polovich, M., White, J. M., & Kelleher, L.O. (eds.) 2005. *Chemotherapy and biotherapy guidelines and recommendations for practice* (2nd. ed.) Pittsburgh, PA: Oncology Nursing Society.

## 16 How Supplied/Storage and Handling

- We suggest using underlining instead of bolded type for the two product formulations.
- *“It is recommended that Valcyte powder for oral solution be constituted by the pharmacist prior to dispensing to the patient [see Dosage and Administration (2.7)].”*

This cross-reference should be to section 2.4.

## 17 Patient Counseling Information

- Because this product has FDA-approved patient labeling, the following line should appear (all in italics, with no brackets) right under the main section title:

*See FDA-Approved Patient Labeling (17.2)*

### 17.1 Information for Patients

- Wherever possible, please revise this section to avoid the use of passive voice and use command language instead (e.g., use “Inform patients of...” instead of “Patients should be informed of...”).

## **17.2 FDA Approved Patient Labeling**

- Please insert a hyphen in “FDA-Approved.”
- Note that the patient labeling is not the subject of this review.

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/s/

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Iris Masucci  
10/14/2008 09:07:11 AM  
DDMAC REVIEWER

Laurie Burke  
10/15/2008 06:29:17 PM  
INTERDISCIPLINARY

**M E M O R A N D U M**

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

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**CLINICAL INSPECTION SUMMARY**

**DATE:** September 30, 2008

**TO:** David Araujo, Regulatory Health Project Manager  
Andreas Pikiş, M. D., Medical Officer  
Division of Antiviral Drug Products

**THROUGH:** Constance Lewin, M.D., M.P.H.  
Branch Chief  
Good Clinical Practice Branch I  
Division of Scientific Investigations

**FROM:** Antoine El-Hage, Ph.D.  
Regulatory Pharmacologist  
Good Clinical Practice Branch I  
Division of Scientific Investigations

**SUBJECT:** Evaluation of Clinical Inspections

**NDA:** 22-257

**APPLICANT:** Hoffmann-La Roche, Inc.

**DRUG:** Valcyte (valganciclovir HCL) P for oral Solution

**NME:** No

**THERAPEUTIC CLASSIFICATION:** Priority Review

**INDICATION:** Male or female solid organ transplant recipients (kidney, (b) (4) heart)  
aged between 1 months and 16 years.

**CONSULTATION REQUEST DATE:** June 2, 2008

**DIVISION ACTION GOAL DATE:** October 31, 2008

**PDUFA DATE:** November 1, 2008

I. BACKGROUND:

The sponsor, Roche, has submitted a new drug application for the use of valganciclovir hydrochloride in the treatment/prevention of Cytomegalovirus disease in high risk heart, (b) (4) and kidney transplant recipients age 1 months to 16years. Subjects will receive oral solution calculated based on body weight and age according to protocol WV1627. Another study submitted by the sponsor to evaluate the safety and tolerability of valganciclovir syrup in the neonatal and infantile populations with symptomatic congenital CMV disease according to protocol DMID01-595. Subjects will take valganciclovir syrup formulation at 14 mg/kg/dose administered twice daily.

The primary objective of study protocol WV1626 is to describe the safety and tolerability profile of valganciclovir oral solution and tablets in pediatric solid organ transplant recipients, to describe the incidence of CMV disease, and to determine the pharmacokinetics of ganciclovir following oral administration of valganciclovir.

The objective of the study protocol DMID01-595 is to determine the pharmacokinetics of ganciclovir following of oral vanciclovir syrup in neonates and young infants with symptomatic congenital CMV disease. The division is interested in the safety profile of the study. The sponsor submitted results from two protocols in support of NDA 22-257.

The inspection targeted three domestic clinical investigators who enrolled a relatively large number of subjects.

II. RESULTS (by protocol/site):

Name of CI, site #and location	Protocol and # of subjects	Inspection Dates	Final Classification
Pablo Sanchez, M.D UT Southwestern Medical Center Department of Pediatrics 5323 Harry Hines Blvd Dallas, TX 75390-9063	DMDI01-595 9 subjects	7/29-31/08	VAI
Robert Ettinger, M.D. UCLA Medical Center 10833 Le Conte Ave Los Angeles, CA 90095	WV16726 5 subjects	7/15-24/08	VAI
S. Paul Hmiel, M.D. Washington University School of Medicine 660 S. Euclid Ave St. Louis, MO 63110	WV16727 5 subjects	8/18-21/08	VAI

Key to Classifications

NAI = No deviations

VAI = Deviation(s) from regulations

OAI = Significant deviations for regulations. Data unreliable.

Pending = Preliminary classification based on e-mail communication from the field; EIR has not been received from the field and complete review of EIR is pending.

Protocol DMDI01-595/CASG109

1. Pablo Sanchez, M.D.  
UT Southwestern medical Center  
Department of Pediatrics  
5323 Harry Hines Blvd.  
Dallas, TX 75390-9063

At this site, a total of 14 subjects were screened; nine subjects were randomized and completed the study. An audit of nine subjects' records was reviewed. There were no subjects enrolled prior to IRB approval of the protocol and informed consent.

The medical records/source data for 9 subjects' files were reviewed in depth and the source data were compared to case report forms, data listings and primary efficacy measures and adverse events. The inspection found an e-mail correspondence at the site noting that for doses 5 through 12 subject #064 received 18.4 mg of the study drug instead of 18 mg. The inspection also found that for subject #064 doses 13 through 25 were missed, and the subject's parent re-dosed the subject for dose 34 due to vomiting. Based on this, data from subject #064 should be excluded from the study. The remaining data from this site for protocol DMID 01-595/CASG 109 appear acceptable in support of the respective indication. There were no limitations to this inspection.

The data appear acceptable in support of the pending application.

Protocol WV16726

2. Robert Ettinger, M.D.  
UCLA Medical Center  
10833 Le Conte Ave  
Los Angeles, California 90095

At this site a total of 6 subjects were screened, 1 subject was reported as screen failure. 5 subjects were randomized and completed the study. Informed consent for all subjects was verified.

The medical records/source data for all 5 subjects' files were reviewed in depth including drug accountability records and compared source documents to data listings and primary efficacy endpoints and adverse events. Our investigation found that subject 8602/G-C violated protocol entry criteria by continuing on the study beyond the protocol maximum 100 days from transplant. Subject 8603 experienced an adverse event of fever due to viral infection and was hospitalized for 8 days. In addition, our investigation found inadequate drug disposition records, in terms of dates and quantity dispensed, amount used and returned by subjects. In general, the records reviewed were accurate in terms of data entries (exception noted above). Our investigation found no significant problem that would impact the results. The clinical investigator/study staff acknowledged the inspectional observations. There were no known limitations to this inspection.

The data appear acceptable in support of the pending application.

3. S. Paul Hmiel, M.D.  
Washington University School of Medicine  
660 S. Euclid Ave  
St. Louis, MO 63110

At this site, a total of 5 subjects were screened, 5 subjects were randomized, 2 subjects withdrew prior to week 26 and 3 subjects completed the study. Informed consent for all subjects was verified.

The medical records/source data for all 5 subject's files were reviewed in depth including drug accountability records and compared source documents to data listings and primary efficacy endpoints and adverse events. Our investigation found that adverse events experienced by subjects 8801, 8803 and 8805 were not reported to the IRB in a timely manner. In general, the records reviewed were accurate in terms of data entries. Our investigation found no significant problem that would impact the results. The clinical investigator/study staff acknowledged the inspectional observations. There were no known limitations to this inspection.

The data appear acceptable in support of the pending application

OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

The inspection of Drs. Sanchez, Ettinger and Hmiel revealed no significant problems that would adversely impact data acceptability. The data submitted from the inspected sites are acceptable in support of the pending application.

*{See appended electronic signature page}*

Antoine El-Hage, Ph.D.  
Regulatory Pharmacologist  
Good Clinical Practice Branch I  
Division of Scientific Investigations

CONCURRENCE:

*{See appended electronic signature page}*

Joseph Salewski/ for  
Constance Lewin, M.D., M.P.H.  
Branch Chief  
Good Clinical Practice Branch I  
Division of Scientific Investigations

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/s/

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Antoine El-Hage  
10/3/2008 01:34:54 PM  
PHARMACOLOGIST

Joseph Salewski  
10/3/2008 02:15:07 PM  
CSO

**NDA REGULATORY FILING REVIEW**  
**(Including Memo of Filing Meeting)**

NDA # 22-257 Supplement # Efficacy Supplement Type SE-

Proprietary Name: Valcyte  
Established Name: valganciclovir Hcl  
Strengths: powder of oral solution 50 mg/ml

Applicant: Hoffmann-La Roche  
Agent for Applicant (if applicable): Snehal Shah

Date of Application: April 30, 2008  
Date of Receipt: May 1, 2008  
Date clock started after UN:  
Date of Filing Meeting: June 25, 2008  
Filing Date: June 30, 2008  
Action Goal Date (optional): October 24, 2008 User Fee Goal Date: November 1, 2008

Indication(s) requested: Treatment of CMV retinitis in patients with AIDS. Prevention of CMV disease in kidney, heart, and kidney-pancrease transplant patients at high risk (Donor CMV seropositive/Recipient CMV seronegative).

Type of Original NDA: (b)(1)  (b)(2)   
AND (if applicable)  
Type of Supplement: (b)(1)  (b)(2)

**NOTE:**

(1) If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application or efficacy supplement is a (b)(2), complete Appendix B.

Review Classification: S  P   
Resubmission after withdrawal?  Resubmission after refuse to file?   
Chemical Classification: (1,2,3 etc.) 3  
Other (orphan, OTC, etc.)

Form 3397 (User Fee Cover Sheet) submitted: YES  NO

User Fee Status: Paid  Exempt (orphan, government)   
Waived (e.g., small business, public health)

**NOTE:** If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required by contacting the User Fee staff in the Office of Regulatory Policy. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the product described in the application.

*Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the User Fee staff.*

- Is there any 5-year or 3-year exclusivity on this active moiety in any approved (b)(1) or (b)(2) application? YES  NO   
If yes, explain:

Note: If the drug under review is a 505(b)(2), this issue will be addressed in detail in appendix B.

- Does another drug have orphan drug exclusivity for the same indication? YES  NO
- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? YES  NO

If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES  NO   
If yes, explain:
- If yes, has OC/DMPQ been notified of the submission? YES  NO
- Does the submission contain an accurate comprehensive index? YES  NO   
If no, explain:
- Was form 356h included with an authorized signature? YES  NO   
**If foreign applicant, both the applicant and the U.S. agent must sign.**
- Submission complete as required under 21 CFR 314.50? YES  NO   
If no, explain:
- Answer 1, 2, or 3 below (do not include electronic content of labeling as an partial electronic submission).

1. This application is a paper NDA YES
2. This application is an eNDA or combined paper + eNDA YES   
This application is: All electronic  Combined paper + eNDA   
This application is in: NDA format  CTD format   
Combined NDA and CTD formats

- Does the eNDA, follow the guidance?  
(<http://www.fda.gov/cder/guidance/2353fnl.pdf>) YES  NO

**If an eNDA, all forms and certifications must be in paper and require a signature.**

If combined paper + eNDA, which parts of the application were submitted in electronic format?

Additional comments:

3. This application is an eCTD NDA. YES

**If an eCTD NDA, all forms and certifications must either be in paper and signed or be electronically signed.**

Additional comments:

- Patent information submitted on form FDA 3542a? YES  NO
- Exclusivity requested? YES, 0.5 Years NO   
*NOTE: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*

- Correctly worded Debarment Certification included with authorized signature? YES  NO   
**If foreign applicant, both the applicant and the U.S. Agent must sign the certification.**

*NOTE: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge . . ."*

- Are the required pediatric assessment studies and/or deferral/partial waiver/full waiver of pediatric studies (or request for deferral/partial waiver/full waiver of pediatric studies) included? YES  NO
- If the submission contains a request for deferral, partial waiver, or full waiver of studies, does the application contain the certification required under FD&C Act sections 505B(a)(3)(B) and (4)(A) and (B)? YES  NO
- Is this submission a partial or complete response to a pediatric Written Request? YES  NO

If yes, contact PMHT in the OND-IO

- Financial Disclosure forms included with authorized signature? YES  NO   
**(Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an agent.)**  
*NOTE: Financial disclosure is required for bioequivalence studies that are the basis for approval.*

- Field Copy Certification (that it is a true copy of the CMC technical section) YES  NO
- PDUFA and Action Goal dates correct in tracking system? YES  NO   
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.

- List referenced IND numbers: 48,106

- Are the trade, established/proper, and applicant names correct in COMIS? YES  NO   
If no, have the Document Room make the corrections.

- End-of-Phase 2 Meeting(s)? Date(s) \_\_\_\_\_ NO   
If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s) Date(s) August 6, 2007 NO   
If yes, distribute minutes before filing meeting.
- Any SPA agreements? Date(s) \_\_\_\_\_ NO   
If yes, distribute letter and/or relevant minutes before filing meeting.

### **Project Management**

- If Rx, was electronic Content of Labeling submitted in SPL format? YES  NO   
If no, request in 74-day letter.
- If Rx, for all new NDAs/efficacy supplements submitted on or after 6/30/06:  
Was the PI submitted in PLR format? YES  NO   
  
If no, explain. Was a waiver or deferral requested before the application was received or in the submission? If before, what is the status of the request:
- If Rx, all labeling (PI, PPI, MedGuide, carton and immediate container labels) has been consulted to DDMAC? YES  NO
- If Rx, trade name (and all labeling) consulted to OSE/DMETS? YES  NO
- If Rx, MedGuide and/or PPI (plus PI) consulted to ODE/DSRCS?  
N/A  YES  NO
- Risk Management Plan consulted to OSE/IO? N/A  YES  NO
- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling submitted? NA  YES  NO

### **If Rx-to-OTC Switch or OTC application:**

- Proprietary name, all OTC labeling/packaging, and current approved PI consulted to OSE/DMETS? YES  NO
- If the application was received by a clinical review division, has DNPCE been notified of the OTC switch application? Or, if received by DNPCE, has the clinical review division been notified? YES  NO

### **Clinical**

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? YES  NO

### **Chemistry**

- Did applicant request categorical exclusion for environmental assessment? YES  NO   
If no, did applicant submit a complete environmental assessment? YES  NO   
If EA submitted, consulted to EA officer, OPS? YES  NO

- Establishment Evaluation Request (EER) submitted to DMPQ? YES  NO
- If a parenteral product, consulted to Microbiology Team? YES  NO

ATTACHMENT

**MEMO OF FILING MEETING**

DATE: June 25, 2008

NDA #: 22-257

DRUG NAMES: Valcyte

APPLICANT: Hoffmann La Roche

BACKGROUND: Roche submits an original NDA to support a new dosage form for Valcyte, Powder for Oral solution 50 mg/ml, for the same approved indication as the Valcyte 450 mg Tablets. (Provide a brief background of the drug, (e.g., molecular entity is already approved and this NDA is for an extended-release formulation; whether another Division is involved; foreign marketing history; etc.)

ATTENDEES: Debra Birnkrant, Jeff Murray, Kendall Marcus, Andreas Piki, Steve Miller, Jules O’Rear, Nilambar Biswal, Peyton Myers, Anita Bigger, Kellie Reynolds, Vikram Arya, and David Araojo

ASSIGNED REVIEWERS (including those not present at filing meeting) :

<u>Discipline/Organization</u>	<u>Reviewer</u>
Medical:	Andreas Piki
Secondary Medical:	Kendall Marcus
Statistical:	Fraser Smith
Pharmacology:	Anita Bigger
Statistical Pharmacology:	
Chemistry:	Ted Chang
Environmental Assessment (if needed):	
Biopharmaceutical:	Vikram Arya
Microbiology, sterility:	
Microbiology, clinical (for antimicrobial products only):	Nilambar Biswal
DSI:	
OPS:	
Regulatory Project Management:	David Araojo
Other Consults:	

Per reviewers, are all parts in English or English translation? YES  NO   
If no, explain:

CLINICAL FILE  REFUSE TO FILE

- Clinical site audit(s) needed? YES  NO   
If no, explain:
- Advisory Committee Meeting needed? YES, date if known \_\_\_\_\_ NO

- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?

N/A  YES  NO

CLINICAL MICROBIOLOGY N/A  FILE  REFUSE TO FILE

STATISTICS N/A  FILE  REFUSE TO FILE

BIOPHARMACEUTICS FILE  REFUSE TO FILE

- Biopharm. study site audits(s) needed?  
YES  NO

PHARMACOLOGY/TOX N/A  FILE  REFUSE TO FILE

- GLP audit needed? YES  NO

CHEMISTRY FILE  REFUSE TO FILE

- Establishment(s) ready for inspection? YES  NO
- Sterile product? YES  NO
- If yes, was microbiology consulted for validation of sterilization? YES  NO

**ELECTRONIC SUBMISSION:**

Any comments:

**REGULATORY CONCLUSIONS/DEFICIENCIES:**

**(Refer to 21 CFR 314.101(d) for filing requirements.)**

- The application is unsuitable for filing. Explain why:
- The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.
  - No filing issues have been identified.
  - Filing issues to be communicated by Day 74. List (optional):

**ACTION ITEMS:**

1.  Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into COMIS.
2.  If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.
3.  If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
4.  If filed, complete the Pediatric Page at this time. (If paper version, enter into DFS.)

5.  Convey document filing issues/no filing issues to applicant by Day 74.

David Araojo  
Regulatory Project Manager

## Appendix A to NDA Regulatory Filing Review

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the

original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),

- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's Office of Regulatory Policy representative.

**Appendix B to NDA Regulatory Filing Review  
Questions for 505(b)(2) Applications**

1. Does the application reference a listed drug (approved drug)? YES  NO

If “No,” skip to question 3.

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #(s):
3. Is this application for a drug that is an “old” antibiotic (as described in the draft guidance implementing the 1997 FDAMA provisions? (Certain antibiotics are not entitled to Hatch-Waxman patent listing and exclusivity benefits.) YES  NO

If “Yes,” skip to question 7.

4. Is this application for a recombinant or biologically-derived product? YES  NO

If “Yes “contact your ODE’s Office of Regulatory Policy representative.

5. The purpose of the questions below (questions 5 to 6) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.
- (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved? YES  NO

*(Pharmaceutical equivalents* are drug products in identical dosage forms that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and (3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))

If “No,” to (a) skip to question 6. Otherwise, answer part (b and (c)).

- (b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval? YES  NO

- (c) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)? YES  NO

If “Yes,” (c), list the pharmaceutical equivalent(s) and proceed to question 6.

If “No,” to (c) list the pharmaceutical equivalent and contact your ODE’s Office of Regulatory Policy representative.

Pharmaceutical equivalent(s):

6. (a) Is there a pharmaceutical alternative(s) already approved? YES  NO

*(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)*

*If “No,” to (a) skip to question 7. Otherwise, answer part (b and (c)).*

- (b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval? YES  NO

- (c) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? YES  NO

*If “Yes,” to (c), proceed to question 7.*

**NOTE:** *If there is more than one pharmaceutical alternative approved, consult your ODE’s Office of Regulatory Policy representative to determine if the appropriate pharmaceutical alternatives are referenced.*

*If “No,” to (c), list the pharmaceutical alternative(s) and contact your ODE’s Office of Regulatory Policy representative. Proceed to question 7.*

Pharmaceutical alternative(s):

7. (a) Does the application rely on published literature necessary to support the proposed approval of the drug product (i.e. is the published literature necessary for the approval)? YES  NO

*If “No,” skip to question 8. Otherwise, answer part (b).*

(b) Does any of the published literature cited reference a specific (e.g. brand name) product? Note that if yes, the applicant will be required to submit patent certification for the product, see question 12.

8. Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, “This application provides for a new indication, otitis media” or “This application provides for a change in dosage form, from capsules to solution”).

9. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA may refuse-to-file such NDAs (see 21 CFR 314.101(d)(9)).) YES  NO

10. Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application may be refused for filing under 21 CFR 314.101(d)(9)). YES  NO

11. Is the application for a duplicate of a listed drug whose only difference is YES  NO

that the rate at which the product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))? If yes, the application may be refused for filing under 21 CFR 314.101(d)(9).

12. Are there certifications for each of the patents listed in the Orange Book for the listed drug(s) referenced by the applicant (see question #2)? (This is different from the patent declaration submitted on form FDA 3542 and 3542a.) YES  NO

13. Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

- Not applicable (e.g., solely based on published literature. See question # 7)
- 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)  
Patent number(s):
- 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)  
Patent number(s):
- 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)  
Patent number(s):
- 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)  
Patent number(s):

**NOTE:** *IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must **subsequently** submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]. The applicant must also submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]. OND will contact you to verify that this documentation was received.*

- 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).  
Patent number(s):
- Written statement from patent owner that it consents to an immediate effective date upon approval of the application.  
Patent number(s):
- 21 CFR 314.50(i)(1)(ii): No relevant patents.
- 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)  
Patent number(s):

14. Did the applicant:

- Identify which parts of the application rely on the finding of safety and effectiveness for a listed drug or published literature describing a listed drug or both? For example, pharm/tox section of application relies on finding of preclinical safety for a listed drug.

YES  NO

*If "Yes," what is the listed drug product(s) and which sections of the 505(b)(2) application rely on the finding of safety and effectiveness or on published literature about that listed drug*

*Was this listed drug product(s) referenced by the applicant? (see question # 2)*

YES  NO

- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug(s)?

N/A  YES  NO

15. (a) Is there unexpired exclusivity on this listed drug (for example, 5 year, 3 year, orphan or pediatric exclusivity)? Note: this information is available in the Orange Book.

YES  NO

If "Yes," please list:

Application No.	Product No.	Exclusivity Code	Exclusivity Expiration

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

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David Araojo  
7/3/2008 09:38:27 AM  
CSO  
Acting CPMS