

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**22-257s000**

**21-304s007**

**ADMINISTRATIVE and CORRESPONDENCE  
DOCUMENTS**

## EXCLUSIVITY SUMMARY

NDA # 21-304

SUPPL # 007

HFD # 530

Trade Name VALCYTE Tablets

Generic Name Valganciclovir

Applicant Name Roche Palo Alto

Approval Date, If Known August 28, 2009

### **PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?**

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES  NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(1) SE 5

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES  NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES  NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

6 months

e) Has pediatric exclusivity been granted for this Active Moiety?

YES  NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

YES

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES  NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

## **PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES**

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES  NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 21-304

VALCYTE Tablet

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES  NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)  
IF "YES," GO TO PART III.

**PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS**

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of

summary for that investigation.

YES  NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES  NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES  NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES  NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES  NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

WP16303, WP 16296, WV16726, and CASG109

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

- a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

|                  |                              |  |
|------------------|------------------------------|--|
| Investigation #1 | YES <input type="checkbox"/> | NO <input checked="" type="checkbox"/> |
| Investigation #2 | YES <input type="checkbox"/> | NO <input checked="" type="checkbox"/> |
| Investigation #3 | YES <input type="checkbox"/> | NO <input checked="" type="checkbox"/> |
| Investigation #4 | YES <input type="checkbox"/> | NO <input checked="" type="checkbox"/> |

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

- b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

|                  |                              |  |
|------------------|------------------------------|--|
| Investigation #1 | YES <input type="checkbox"/> | NO <input checked="" type="checkbox"/> |
| Investigation #2 | YES <input type="checkbox"/> | NO <input checked="" type="checkbox"/> |

Investigation #3 YES  NO

Investigation #4 YES  NO

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

WP16303, WP16296, WV16726, and CASG109

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 - 3 !  
IND # 48,106 YES  ! NO   
! Explain:

Investigation # 4 !  
IND # 63389 YES  ! NO   
! Explain:  
CASG109 was done under an NIAID IND

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1-3

YES

Explain:

!

!

! NO

! Explain:

Investigation #4

YES

Explain:

!

!

! NO

! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES

NO

If yes, explain:

=====

Name of person completing form: Karen Winestock

Title: Chief, Regulatory Project Management Staff

Date: 12/8/09

Name of Office/Division Director signing form: DAVP (HFD-530)/Debra Birnkrant, M.D.

Title: Division Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

| Application Type/Number | Submission Type/Number | Submitter Name      | Product Name                             |
|-------------------------|------------------------|---------------------|--|
| NDA-21304               | SUPPL-7                | ROCHE PALO ALTO LLC | VALCYTE(VALGANCICLOVIR HYDROCHLORIDE)450 |

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

/s/

KAREN D WINESTOCK  
01/05/2010

DEBRA B BIRNKRANT  
01/05/2010

## EXCLUSIVITY SUMMARY

NDA # 22-257

SUPPL # 000

HFD # 530

Trade Name VALCYTE

Generic Name Valganciclovir

Applicant Name Hoffman La Roche, Inc

Approval Date, If Known August 28, 2009

### **PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?**

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YES  NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES  NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES  NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

6 months

e) Has pediatric exclusivity been granted for this Active Moiety?

YES  NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

YES

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES  NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

## **PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES**

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES  NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 21-304

VALCYTE tablet

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES  NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

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summary for that investigation.

YES  NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES  NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES  NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES  NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES  NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

WP16302, WP16303, WP16296, WV16726, and CASG109

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

- a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES  NO

Investigation #2 YES  NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

- b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES  NO

Investigation #2 YES  NO

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

WP16302, WP16303, WP16296, WV16726, and CASG109

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1  
IND # 48,106      YES       ! NO   
! Explain:

Investigation #2  
IND # 48,106      YES       ! NO   
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES

Explain:

!

!

! NO

! Explain:

Investigation #2

YES

Explain:

!

!

! NO

! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES

NO

If yes, explain:

=====

Name of person completing form: Jaewon Hong, PharmD

Title: Regulatory Project Manager

Date: 8/28/2009

Name of Office/Division Director signing form: DAVP (HFD-530)/Debra Birnkrant, M.D.

Title: Division Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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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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JAEWON HONG  
09/04/2009

DEBRA B BIRNKRANT  
09/04/2009

**PEDIATRIC PAGE**

**(Complete for all filed original applications and efficacy supplements)**

NDA/BLA#: 22-257

Supplement Number: \_\_\_\_\_

NDA Supplement Type (e.g. SE5): \_\_\_\_\_

Division Name: DAVP

PDUFA Goal Date: 11/1/08

Stamp Date: 5/1/2008

Proprietary Name: Valcyte

Established/Generic Name: valganciclovir hydrochloride

Dosage Form: powder for oral solution

Applicant/Sponsor: Roche

Indication(s) previously approved (please complete this question for supplements and Type 6 NDAs only):

(1) Treatment of cytomegalovirus (CMV) retinitis in patients with acquired immunodeficiency syndrome (AIDS)

(2) Prevention of cytomegalovirus (CMV) disease in kidney, heart, and kidney-pancreas transplant patients at high risk (Donor CMV seropositive/Recipient CMV seronegative [(D+/R-)])

(3) \_\_\_\_\_

(4) \_\_\_\_\_

Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s): 2

(Attach a completed Pediatric Page for each indication in current application.)

**Indication:** Prevention of cytomegalovirus (CMV) disease in kidney, heart, and kidney-pancreas transplant patients at high risk

**Q1:** Is this application in response to a PREA PMR? Yes  Continue

No  Please proceed to Question 2.

If Yes, NDA/BLA#: 21-304

Supplement #: \_\_\_\_\_

PMR #: \_\_\_\_\_

Does the division agree that this is a complete response to the PMR?

Yes. Please proceed to Section D.

No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

**Q2:** Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

(a) NEW  active ingredient(s) (includes new combination);  indication(s);  dosage form;  dosing regimen; or  route of administration?\*

(b)  No. PREA does not apply. **Skip to signature block.**

\* **Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.**

**Q3:** Does this indication have orphan designation?

Yes. PREA does not apply. **Skip to signature block.**

No. Please proceed to the next question.

**Q4:** Is there a full waiver for all pediatric age groups for this indication (check one)?

Yes: (Complete Section A.)

No: Please check all that apply:

Partial Waiver for selected pediatric subpopulations (Complete Sections B)

Deferred for some or all pediatric subpopulations (Complete Sections C)

Completed for some or all pediatric subpopulations (Complete Sections D)

Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)

Extrapolation in One or More Pediatric Age Groups (Complete Section F)

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL ([cdcrpmhs@fda.hhs.gov](mailto:cdcrpmhs@fda.hhs.gov)) OR AT 301-796-0700.

(Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

**Section A: Fully Waived Studies (for all pediatric age groups)**

Reason(s) for full waiver: (check, and attach a brief justification for the reason(s) selected)

- Necessary studies would be impossible or highly impracticable because:
  - Disease/condition does not exist in children
  - Too few children with disease/condition to study
  - Other (e.g., patients geographically dispersed): \_\_\_\_\_
- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (Note: if studies are fully waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (Note: if studies are fully waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (Note: if studies are fully waived on this ground, this information must be included in the labeling.)
- Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

**Section B: Partially Waived Studies (for selected pediatric subpopulations)**

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

|                          |         |               | Reason (see below for further detail): |   |                                    |                                 |                          |
|--------------------------|---------|---------------|--|---|------------------------------------|---------------------------------|--------------------------|
|                          | minimum | maximum       | Not feasible <sup>#</sup>              | Not meaningful therapeutic benefit <sup>*</sup> | Ineffective or unsafe <sup>†</sup> | Formulation failed <sup>Δ</sup> |                          |
| <input type="checkbox"/> | Neonate | __ wk. __ mo. | __ wk. __ mo.                          | <input type="checkbox"/>                        | <input type="checkbox"/>           | <input type="checkbox"/>        | <input type="checkbox"/> |
| <input type="checkbox"/> | Other   | __ yr. __ mo. | __ yr. __ mo.                          | <input type="checkbox"/>                        | <input type="checkbox"/>           | <input type="checkbox"/>        | <input type="checkbox"/> |
| <input type="checkbox"/> | Other   | __ yr. __ mo. | __ yr. __ mo.                          | <input type="checkbox"/>                        | <input type="checkbox"/>           | <input type="checkbox"/>        | <input type="checkbox"/> |
| <input type="checkbox"/> | Other   | __ yr. __ mo. | __ yr. __ mo.                          | <input type="checkbox"/>                        | <input type="checkbox"/>           | <input type="checkbox"/>        | <input type="checkbox"/> |
| <input type="checkbox"/> | Other   | __ yr. __ mo. | __ yr. __ mo.                          | <input type="checkbox"/>                        | <input type="checkbox"/>           | <input type="checkbox"/>        | <input type="checkbox"/> |

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

Reason(s) for partial waiver (check reason corresponding to the category checked above, and attach a brief justification):

# Not feasible:

- Necessary studies would be impossible or highly impracticable because:
  - Disease/condition does not exist in children
  - Too few children with disease/condition to study
  - Other (e.g., patients geographically dispersed): \_\_\_\_\_

\* Not meaningful therapeutic benefit:

- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of

pediatric patients in this/these pediatric subpopulation(s).

**;** Ineffective or unsafe:

- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

**Δ** Formulation failed:

- Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.*)

Justification attached.

*For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.*

**Section C: Deferred Studies (for selected pediatric subpopulations).**

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

| Deferrals (for each or all age groups):            |               |               | Reason for Deferral          |   |   | Applicant Certification † |
|--|---------------|---------------|------------------------------|---|---|---------------------------|
| Population   | minimum       | maximum       | Ready for Approval in Adults | Need Additional Adult Safety or Efficacy Data | Other Appropriate Reason (specify below)* | Received                  |
| <input type="checkbox"/> Neonate                   | __ wk. __ mo. | __ wk. __ mo. | <input type="checkbox"/>     | <input type="checkbox"/>                      | <input type="checkbox"/>                  | <input type="checkbox"/>  |
| <input type="checkbox"/> Other                     | __ yr. __ mo. | __ yr. __ mo. | <input type="checkbox"/>     | <input type="checkbox"/>                      | <input type="checkbox"/>                  | <input type="checkbox"/>  |
| <input type="checkbox"/> Other                     | __ yr. __ mo. | __ yr. __ mo. | <input type="checkbox"/>     | <input type="checkbox"/>                      | <input type="checkbox"/>                  | <input type="checkbox"/>  |
| <input type="checkbox"/> Other                     | __ yr. __ mo. | __ yr. __ mo. | <input type="checkbox"/>     | <input type="checkbox"/>                      | <input type="checkbox"/>                  | <input type="checkbox"/>  |
| <input type="checkbox"/> Other                     | __ yr. __ mo. | __ yr. __ mo. | <input type="checkbox"/>     | <input type="checkbox"/>                      | <input type="checkbox"/>                  | <input type="checkbox"/>  |
| <input type="checkbox"/> All Pediatric Populations | 0 yr. 0 mo.   | 16 yr. 11 mo. | <input type="checkbox"/>     | <input type="checkbox"/>                      | <input type="checkbox"/>                  | <input type="checkbox"/>  |
| Date studies are due (mm/dd/yy): _____             |               |               |                              |   |   |                           |

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

\* Other Reason: \_\_\_\_\_

*f Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)*

*If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.*

**Section D: Completed Studies (for some or all pediatric subpopulations).**

| Pediatric subpopulation(s) in which studies have been completed (check below): |                              |               |               |   |                             |
|--|------------------------------|---------------|---------------|---|-----------------------------|
| Population   |                              | minimum       | maximum       | PeRC Pediatric Assessment form attached?. |                             |
| <input type="checkbox"/>   | Neonate                      | __ wk. __ mo. | __ wk. __ mo. | Yes <input type="checkbox"/>              | No <input type="checkbox"/> |
| <input checked="" type="checkbox"/>  | Other                        | 0 yr. 4 mo.   | 16 yr. 0 mo.  | Yes <input checked="" type="checkbox"/>   | No <input type="checkbox"/> |
| <input type="checkbox"/>   | Other                        | __ yr. __ mo. | __ yr. __ mo. | Yes <input type="checkbox"/>              | No <input type="checkbox"/> |
| <input type="checkbox"/>   | Other                        | __ yr. __ mo. | __ yr. __ mo. | Yes <input type="checkbox"/>              | No <input type="checkbox"/> |
| <input type="checkbox"/>   | Other                        | __ yr. __ mo. | __ yr. __ mo. | Yes <input type="checkbox"/>              | No <input type="checkbox"/> |
| <input type="checkbox"/>   | All Pediatric Subpopulations | 0 yr. 0 mo.   | 16 yr. 11 mo. | Yes <input type="checkbox"/>              | No <input type="checkbox"/> |

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

*Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.*

**Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):**

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:

| Population               |                              | minimum       | maximum       |
|--------------------------|------------------------------|---------------|---------------|
| <input type="checkbox"/> | Neonate                      | __ wk. __ mo. | __ wk. __ mo. |
| <input type="checkbox"/> | Other                        | __ yr. __ mo. | __ yr. __ mo. |
| <input type="checkbox"/> | Other                        | __ yr. __ mo. | __ yr. __ mo. |
| <input type="checkbox"/> | Other                        | __ yr. __ mo. | __ yr. __ mo. |
| <input type="checkbox"/> | Other                        | __ yr. __ mo. | __ yr. __ mo. |
| <input type="checkbox"/> | All Pediatric Subpopulations | 0 yr. 0 mo.   | 16 yr. 11 mo. |

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

*If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.*

**Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)**

*Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.*

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

| Population               |                              | minimum       | maximum       | Extrapolated from:       |                          |
|--------------------------|------------------------------|---------------|---------------|--------------------------|--------------------------|
|                          |                              |               |               | Adult Studies?           | Other Pediatric Studies? |
| <input type="checkbox"/> | Neonate                      | __ wk. __ mo. | __ wk. __ mo. | <input type="checkbox"/> | <input type="checkbox"/> |
| <input type="checkbox"/> | Other                        | __ yr. __ mo. | __ yr. __ mo. | <input type="checkbox"/> | <input type="checkbox"/> |
| <input type="checkbox"/> | Other                        | __ yr. __ mo. | __ yr. __ mo. | <input type="checkbox"/> | <input type="checkbox"/> |
| <input type="checkbox"/> | Other                        | __ yr. __ mo. | __ yr. __ mo. | <input type="checkbox"/> | <input type="checkbox"/> |
| <input type="checkbox"/> | Other                        | __ yr. __ mo. | __ yr. __ mo. | <input type="checkbox"/> | <input type="checkbox"/> |
| <input type="checkbox"/> | All Pediatric Subpopulations | 0 yr. 0 mo.   | 16 yr. 11 mo. | <input type="checkbox"/> | <input type="checkbox"/> |

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

*Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.*

**IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL ([cderpms@fda.hhs.gov](mailto:cderpms@fda.hhs.gov)) OR AT 301-796-0700.**

*If there are additional indications, please complete the attachment for each one of those indications. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS or DARRTS as appropriate after clearance by PeRC.*

This page was completed by:

*{See appended electronic signature page}*

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Regulatory Project Manager

(Revised: 6/2008)

**NOTE: If you have no other indications for this application, you may delete the attachments from this document.**

**Attachment A**

(This attachment is to be completed for those applications with multiple indications only.)

**Indication #2: Treatment of cytomegalovirus (CMV) retinitis in patients with acquired immunodeficiency syndrome (AIDS)****Q1:** Does this indication have orphan designation?

- Yes. PREA does not apply. **Skip to signature block.**
- No. Please proceed to the next question.

**Q2:** Is there a full waiver for all pediatric age groups for this indication (check one)?

- Yes: (Complete Section A.)
- No: Please check all that apply:
- Partial Waiver for selected pediatric subpopulations (Complete Sections B)
  - Deferred for some or all pediatric subpopulations (Complete Sections C)
  - Completed for some or all pediatric subpopulations (Complete Sections D)
  - Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
  - Extrapolation in One or More Pediatric Age Groups (Complete Section F)
- (Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

**Section A: Fully Waived Studies (for all pediatric age groups)**

Reason(s) for full waiver: (check, and attach a brief justification for the reason(s) selected)

- Necessary studies would be impossible or highly impracticable because:
- Disease/condition does not exist in children
  - Too few children with disease/condition to study
  - Other (e.g., patients geographically dispersed): \_\_\_\_\_
- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Justification attached.

*If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.*

**Section B: Partially Waived Studies (for selected pediatric subpopulations)**

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

|                          |         | Reason (see below for further detail): |               |                           |   |                                    |                                 |
|--------------------------|---------|--|---------------|---------------------------|---|------------------------------------|---------------------------------|
|                          |         | minimum                                | maximum       | Not feasible <sup>#</sup> | Not meaningful therapeutic benefit <sup>*</sup> | Ineffective or unsafe <sup>†</sup> | Formulation failed <sup>Δ</sup> |
| <input type="checkbox"/> | Neonate | __ wk. __ mo.                          | __ wk. __ mo. | <input type="checkbox"/>  | <input type="checkbox"/>                        | <input type="checkbox"/>           | <input type="checkbox"/>        |
| <input type="checkbox"/> | Other   | __ yr. __ mo.                          | __ yr. __ mo. | <input type="checkbox"/>  | <input type="checkbox"/>                        | <input type="checkbox"/>           | <input type="checkbox"/>        |
| <input type="checkbox"/> | Other   | __ yr. __ mo.                          | __ yr. __ mo. | <input type="checkbox"/>  | <input type="checkbox"/>                        | <input type="checkbox"/>           | <input type="checkbox"/>        |
| <input type="checkbox"/> | Other   | __ yr. __ mo.                          | __ yr. __ mo. | <input type="checkbox"/>  | <input type="checkbox"/>                        | <input type="checkbox"/>           | <input type="checkbox"/>        |
| <input type="checkbox"/> | Other   | __ yr. __ mo.                          | __ yr. __ mo. | <input type="checkbox"/>  | <input type="checkbox"/>                        | <input type="checkbox"/>           | <input type="checkbox"/>        |

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

# Not feasible:

- Necessary studies would be impossible or highly impracticable because:
  - Disease/condition does not exist in children
  - Too few children with disease/condition to study
  - Other (e.g., patients geographically dispersed): \_\_\_\_\_

\* Not meaningful therapeutic benefit:

- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)

Δ Formulation failed:

- Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)

Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Section C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so,

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL ([cderpms@fda.hhs.gov](mailto:cderpms@fda.hhs.gov)) OR AT 301-796-0700.

Proceed to Section F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

**Section C: Deferred Studies (for some or all pediatric subpopulations).**

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

| Deferrals (for each or all age groups):            |               |               | Reason for Deferral          |   |   | Applicant Certification † |
|--|---------------|---------------|------------------------------|---|---|---------------------------|
| Population   | minimum       | maximum       | Ready for Approval in Adults | Need Additional Adult Safety or Efficacy Data | Other Appropriate Reason (specify below)* | Received                  |
| <input type="checkbox"/> Neonate                   | __ wk. __ mo. | __ wk. __ mo. | <input type="checkbox"/>     | <input type="checkbox"/>                      | <input type="checkbox"/>                  | <input type="checkbox"/>  |
| <input type="checkbox"/> Other                     | __ yr. __ mo. | __ yr. __ mo. | <input type="checkbox"/>     | <input type="checkbox"/>                      | <input type="checkbox"/>                  | <input type="checkbox"/>  |
| <input type="checkbox"/> Other                     | __ yr. __ mo. | __ yr. __ mo. | <input type="checkbox"/>     | <input type="checkbox"/>                      | <input type="checkbox"/>                  | <input type="checkbox"/>  |
| <input type="checkbox"/> Other                     | __ yr. __ mo. | __ yr. __ mo. | <input type="checkbox"/>     | <input type="checkbox"/>                      | <input type="checkbox"/>                  | <input type="checkbox"/>  |
| <input type="checkbox"/> Other                     | __ yr. __ mo. | __ yr. __ mo. | <input type="checkbox"/>     | <input type="checkbox"/>                      | <input type="checkbox"/>                  | <input type="checkbox"/>  |
| <input type="checkbox"/> All Pediatric Populations | 0 yr. 0 mo.   | 16 yr. 11 mo. | <input type="checkbox"/>     | <input type="checkbox"/>                      | <input type="checkbox"/>                  | <input type="checkbox"/>  |
| Date studies are due (mm/dd/yy): _____             |               |               |                              |   |   |                           |

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

\* Other Reason: \_\_\_\_\_

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

**Section D: Completed Studies (for some or all pediatric subpopulations).**

| Pediatric subpopulation(s) in which studies have been completed (check below): |                              |               |               |  |                             |
|--|------------------------------|---------------|---------------|--|-----------------------------|
| Population   |                              | minimum       | maximum       | PeRC Pediatric Assessment form attached? |                             |
| <input type="checkbox"/>   | Neonate                      | __ wk. __ mo. | __ wk. __ mo. | Yes <input type="checkbox"/>             | No <input type="checkbox"/> |
| <input type="checkbox"/>   | Other                        | __ yr. __ mo. | __ yr. __ mo. | Yes <input type="checkbox"/>             | No <input type="checkbox"/> |
| <input type="checkbox"/>   | Other                        | __ yr. __ mo. | __ yr. __ mo. | Yes <input type="checkbox"/>             | No <input type="checkbox"/> |
| <input type="checkbox"/>   | Other                        | __ yr. __ mo. | __ yr. __ mo. | Yes <input type="checkbox"/>             | No <input type="checkbox"/> |
| <input type="checkbox"/>   | Other                        | __ yr. __ mo. | __ yr. __ mo. | Yes <input type="checkbox"/>             | No <input type="checkbox"/> |
| <input type="checkbox"/>   | All Pediatric Subpopulations | 0 yr. 0 mo.   | 16 yr. 11 mo. | Yes <input type="checkbox"/>             | No <input type="checkbox"/> |

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

*Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.*

**Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):**

| Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed: |                              |               |               |
|--|------------------------------|---------------|---------------|
| Population   |                              | minimum       | maximum       |
| <input type="checkbox"/>   | Neonate                      | __ wk. __ mo. | __ wk. __ mo. |
| <input type="checkbox"/>   | Other                        | __ yr. __ mo. | __ yr. __ mo. |
| <input type="checkbox"/>   | Other                        | __ yr. __ mo. | __ yr. __ mo. |
| <input type="checkbox"/>   | Other                        | __ yr. __ mo. | __ yr. __ mo. |
| <input type="checkbox"/>   | Other                        | __ yr. __ mo. | __ yr. __ mo. |
| <input type="checkbox"/>   | All Pediatric Subpopulations | 0 yr. 0 mo.   | 16 yr. 11 mo. |

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

*If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.*

**Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)**

*Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.*

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

| Population  | minimum       | maximum       | Extrapolated from:       |                          |
|---|---------------|---------------|--------------------------|--------------------------|
|   |               |               | Adult Studies?           | Other Pediatric Studies? |
| <input type="checkbox"/> Neonate                      | __ wk. __ mo. | __ wk. __ mo. | <input type="checkbox"/> | <input type="checkbox"/> |
| <input type="checkbox"/> Other                        | __ yr. __ mo. | __ yr. __ mo. | <input type="checkbox"/> | <input type="checkbox"/> |
| <input type="checkbox"/> Other                        | __ yr. __ mo. | __ yr. __ mo. | <input type="checkbox"/> | <input type="checkbox"/> |
| <input type="checkbox"/> Other                        | __ yr. __ mo. | __ yr. __ mo. | <input type="checkbox"/> | <input type="checkbox"/> |
| <input type="checkbox"/> Other                        | __ yr. __ mo. | __ yr. __ mo. | <input type="checkbox"/> | <input type="checkbox"/> |
| <input type="checkbox"/> All Pediatric Subpopulations | 0 yr. 0 mo.   | 16 yr. 11 mo. | <input type="checkbox"/> | <input type="checkbox"/> |

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

*Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.*

**If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS or DARRTS as appropriate after clearance by PeRC.**

**This page was completed by:**

{See appended electronic signature page}

**Regulatory Project Manager**

**FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700**

(Revised: 6/2008)

**Attachment B**

(This attachment is to be completed for those applications with multiple indications only.)

**Indication #3:** (b) (4)

**Q1:** Does this indication have orphan designation?

- Yes. PREA does not apply. **Skip to signature block.**
- No. Please proceed to the next question.

**Q2:** Is there a full waiver for all pediatric age groups for this indication (check one)?

- Yes: (Complete Section A.)
  - No: Please check all that apply:
    - Partial Waiver for selected pediatric subpopulations (Complete Sections B)
    - Deferred for some or all pediatric subpopulations (Complete Sections C)
    - Completed for some or all pediatric subpopulations (Complete Sections D)
    - Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
    - Extrapolation in One or More Pediatric Age Groups (Complete Section F)
- (Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

**Section A: Fully Waived Studies (for all pediatric age groups)**

Reason(s) for full waiver: (check, and attach a brief justification for the reason(s) selected)

- Necessary studies would be impossible or highly impracticable because:
  - Disease/condition does not exist in children
  - Too few children with disease/condition to study
  - Other (e.g., patients geographically dispersed): \_\_\_\_\_
- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Justification attached.

*If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.*

**Section B: Partially Waived Studies (for selected pediatric subpopulations)**

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

|                          |         | Reason (see below for further detail): |               |                           |   |                                    |                                 |
|--------------------------|---------|--|---------------|---------------------------|---|------------------------------------|---------------------------------|
|                          |         | minimum                                | maximum       | Not feasible <sup>#</sup> | Not meaningful therapeutic benefit <sup>*</sup> | Ineffective or unsafe <sup>†</sup> | Formulation failed <sup>Δ</sup> |
| <input type="checkbox"/> | Neonate | __ wk. __ mo.                          | __ wk. __ mo. | <input type="checkbox"/>  | <input type="checkbox"/>                        | <input type="checkbox"/>           | <input type="checkbox"/>        |
| <input type="checkbox"/> | Other   | __ yr. __ mo.                          | __ yr. __ mo. | <input type="checkbox"/>  | <input type="checkbox"/>                        | <input type="checkbox"/>           | <input type="checkbox"/>        |
| <input type="checkbox"/> | Other   | __ yr. __ mo.                          | __ yr. __ mo. | <input type="checkbox"/>  | <input type="checkbox"/>                        | <input type="checkbox"/>           | <input type="checkbox"/>        |
| <input type="checkbox"/> | Other   | __ yr. __ mo.                          | __ yr. __ mo. | <input type="checkbox"/>  | <input type="checkbox"/>                        | <input type="checkbox"/>           | <input type="checkbox"/>        |
| <input type="checkbox"/> | Other   | __ yr. __ mo.                          | __ yr. __ mo. | <input type="checkbox"/>  | <input type="checkbox"/>                        | <input type="checkbox"/>           | <input type="checkbox"/>        |

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

Reason(s) for partial waiver (check reason corresponding to the category checked above, and attach a brief justification):

# Not feasible:

Necessary studies would be impossible or highly impracticable because:

- Disease/condition does not exist in children
- Too few children with disease/condition to study
- Other (e.g., patients geographically dispersed): \_\_\_\_\_

\* Not meaningful therapeutic benefit:

Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)

Δ Formulation failed:

Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)

Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Section C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so,

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL ([cderpms@fda.hhs.gov](mailto:cderpms@fda.hhs.gov)) OR AT 301-796-0700.

proceed to Section F).. Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

**Section C: Deferred Studies (for some or all pediatric subpopulations).**

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

| Deferrals (for each or all age groups):            |               |               | Reason for Deferral          |   |   | Applicant Certification † |
|--|---------------|---------------|------------------------------|---|---|---------------------------|
| Population   | minimum       | maximum       | Ready for Approval in Adults | Need Additional Adult Safety or Efficacy Data | Other Appropriate Reason (specify below)* | Received                  |
| <input type="checkbox"/> Neonate                   | __ wk. __ mo. | __ wk. __ mo. | <input type="checkbox"/>     | <input type="checkbox"/>                      | <input type="checkbox"/>                  | <input type="checkbox"/>  |
| <input type="checkbox"/> Other                     | __ yr. __ mo. | __ yr. __ mo. | <input type="checkbox"/>     | <input type="checkbox"/>                      | <input type="checkbox"/>                  | <input type="checkbox"/>  |
| <input type="checkbox"/> Other                     | __ yr. __ mo. | __ yr. __ mo. | <input type="checkbox"/>     | <input type="checkbox"/>                      | <input type="checkbox"/>                  | <input type="checkbox"/>  |
| <input type="checkbox"/> Other                     | __ yr. __ mo. | __ yr. __ mo. | <input type="checkbox"/>     | <input type="checkbox"/>                      | <input type="checkbox"/>                  | <input type="checkbox"/>  |
| <input type="checkbox"/> Other                     | __ yr. __ mo. | __ yr. __ mo. | <input type="checkbox"/>     | <input type="checkbox"/>                      | <input type="checkbox"/>                  | <input type="checkbox"/>  |
| <input type="checkbox"/> All Pediatric Populations | 0 yr. 0 mo.   | 16 yr. 11 mo. | <input type="checkbox"/>     | <input type="checkbox"/>                      | <input type="checkbox"/>                  | <input type="checkbox"/>  |
| Date studies are due (mm/dd/yy): _____             |               |               |                              |   |   |                           |

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

\* Other Reason: \_\_\_\_\_

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

**Section D: Completed Studies (for some or all pediatric subpopulations).**

| Pediatric subpopulation(s) in which studies have been completed (check below): |                              |               |               |  |                             |
|--|------------------------------|---------------|---------------|--|-----------------------------|
| Population   |                              | minimum       | maximum       | PeRC Pediatric Assessment form attached? |                             |
| <input checked="" type="checkbox"/>  | Neonate                      | 0 wk. __ mo.  | __ wk. 3 mo.  | Yes <input checked="" type="checkbox"/>  | No <input type="checkbox"/> |
| <input type="checkbox"/>   | Other                        | __ yr. __ mo. | __ yr. __ mo. | Yes <input type="checkbox"/>             | No <input type="checkbox"/> |
| <input type="checkbox"/>   | Other                        | __ yr. __ mo. | __ yr. __ mo. | Yes <input type="checkbox"/>             | No <input type="checkbox"/> |
| <input type="checkbox"/>   | Other                        | __ yr. __ mo. | __ yr. __ mo. | Yes <input type="checkbox"/>             | No <input type="checkbox"/> |
| <input type="checkbox"/>   | Other                        | __ yr. __ mo. | __ yr. __ mo. | Yes <input type="checkbox"/>             | No <input type="checkbox"/> |
| <input type="checkbox"/>   | All Pediatric Subpopulations | 0 yr. 0 mo.   | 16 yr. 11 mo. | Yes <input type="checkbox"/>             | No <input type="checkbox"/> |

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

*Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.*

**Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):**

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:

| Population               |                              | minimum       | maximum       |
|--------------------------|------------------------------|---------------|---------------|
| <input type="checkbox"/> | Neonate                      | __ wk. __ mo. | __ wk. __ mo. |
| <input type="checkbox"/> | Other                        | __ yr. __ mo. | __ yr. __ mo. |
| <input type="checkbox"/> | Other                        | __ yr. __ mo. | __ yr. __ mo. |
| <input type="checkbox"/> | Other                        | __ yr. __ mo. | __ yr. __ mo. |
| <input type="checkbox"/> | Other                        | __ yr. __ mo. | __ yr. __ mo. |
| <input type="checkbox"/> | All Pediatric Subpopulations | 0 yr. 0 mo.   | 16 yr. 11 mo. |

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

*If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.*

**Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)**

*Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition **AND** (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.*

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

| Population  | minimum       | maximum       | Extrapolated from:       |                          |
|---|---------------|---------------|--------------------------|--------------------------|
|   |               |               | Adult Studies?           | Other Pediatric Studies? |
| <input type="checkbox"/> Neonate                      | __ wk. __ mo. | __ wk. __ mo. | <input type="checkbox"/> | <input type="checkbox"/> |
| <input type="checkbox"/> Other                        | __ yr. __ mo. | __ yr. __ mo. | <input type="checkbox"/> | <input type="checkbox"/> |
| <input type="checkbox"/> Other                        | __ yr. __ mo. | __ yr. __ mo. | <input type="checkbox"/> | <input type="checkbox"/> |
| <input type="checkbox"/> Other                        | __ yr. __ mo. | __ yr. __ mo. | <input type="checkbox"/> | <input type="checkbox"/> |
| <input type="checkbox"/> Other                        | __ yr. __ mo. | __ yr. __ mo. | <input type="checkbox"/> | <input type="checkbox"/> |
| <input type="checkbox"/> All Pediatric Subpopulations | 0 yr. 0 mo.   | 16 yr. 11 mo. | <input type="checkbox"/> | <input type="checkbox"/> |

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

*Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.*

**If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS or DARRTS as appropriate after clearance by PeRC.**

**This page was completed by:**

{See appended electronic signature page}

\_\_\_\_\_  
**Regulatory Project Manager**

**FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700**

**(Revised: 6/2008)**

**DEBARMENT CERTIFICATION**

Hoffmann-La Roche Inc. 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.

## ACTION PACKAGE CHECKLIST

| APPLICATION INFORMATION <sup>1</sup>  |                                    |   |
|---|------------------------------------|---|
| NDA # 22-257/Original-1<br>NDA 21-304 S-07<br>BLA #   | NDA Supplement # S-07<br>BLA STN # | If NDA, Efficacy Supplement Type: New patient population  |
| Proprietary Name: VALCYTE<br>Established/Proper Name: Valganciclovir<br>Dosage Form: Powder for oral solution   |                                    | Applicant: Roche Palo Alto LLC<br>Agent for Applicant (if applicable): Wendy Corbett, Ph.D  |
| RPM: Jaewon Hong  |                                    | Division: Division of Antiviral Products  |
| <p><b>NDA:</b><br/>                     NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1)   <input type="checkbox"/> 505(b)(2)<br/>                     Efficacy Supplement:   <input checked="" type="checkbox"/> 505(b)(1)   <input type="checkbox"/> 505(b)(2)</p> <p>(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). Consult page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)</p> |                                    | <p><b>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</b><br/>                     Listed drug(s) referred to in 505(b)(2) application (include NDA/ANDA #(s) and drug name(s)):</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p><input type="checkbox"/> If no listed drug, check here and explain:</p> <p><b>Prior to approval, review and confirm the information previously provided in Appendix B to the Regulatory Filing Review by re-checking the Orange Book for any new patents and pediatric exclusivity. If there are any changes in patents or exclusivity, notify the OND ADRA immediately and complete a new Appendix B of the Regulatory Filing Review.</b></p> <p style="text-align: center;"> <input type="checkbox"/> No changes                      <input type="checkbox"/> Updated<br/>                     Date of check:                 </p> <p><b>If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</b></p> <p><b>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</b></p> |
| ❖ User Fee Goal Date<br>Action Goal Date (if different)   |                                    | August 28, 2009   |
| ❖ Actions   |                                    |   |
| <ul style="list-style-type: none"> <li>• Proposed action</li> </ul>   |                                    | <input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> AE<br><input type="checkbox"/> NA <input type="checkbox"/> CR   |
| <ul style="list-style-type: none"> <li>• Previous actions (<i>specify type and date for each action taken</i>)</li> </ul>   |                                    | <input type="checkbox"/> None Complete Response<br>November 25, 2008  |

<sup>1</sup> The **Application Information** section is (only) a checklist. The **Contents of Action Package** section (beginning on page 5) lists the documents to be included in the Action Package.

❖ Promotional Materials (*accelerated approvals only*)  
Note: If accelerated approval (21 CFR 314.510/601.41), promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see guidance <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf>). If not submitted, explain \_\_\_\_\_

Received

|   |   |
|---|---|
| ❖ Application Characteristics <sup>2</sup>  |   |
| <p>Review priority: <input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority<br/>         Chemical classification (new NDAs only):</p> <p><input type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch<br/> <input type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch<br/> <input type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC</p> <p>NDAs: Subpart H <span style="margin-left: 200px;">BLAs: Subpart E</span><br/> <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <span style="margin-left: 100px;"><input type="checkbox"/> Accelerated approval (21 CFR 601.41)</span><br/> <input type="checkbox"/> Restricted distribution (21 CFR 314.520) <span style="margin-left: 100px;"><input type="checkbox"/> Restricted distribution (21 CFR 601.42)</span><br/>         Subpart I <span style="margin-left: 200px;">Subpart H</span><br/> <input type="checkbox"/> Approval based on animal studies <span style="margin-left: 100px;"><input type="checkbox"/> Approval based on animal studies</span></p> <p><input type="checkbox"/> Submitted in response to a PMR<br/> <input type="checkbox"/> Submitted in response to a PMC</p> <p>Comments: <u>Submitted in response to PWR</u></p> |   |
| ❖ Date reviewed by PeRC ( <i>required for approvals only</i> )<br>If PeRC review not necessary, explain: _____  | July 24, 2008   |
| ❖ BLAs only: <i>RMS-BLA Product Information Sheet for TBP</i> has been completed and forwarded to OBPS/DRM ( <i>approvals only</i> )  | <input type="checkbox"/> Yes, date  |
| ❖ BLAs only: is the product subject to official FDA lot release per 21 CFR 610.2 ( <i>approvals only</i> )  | <input type="checkbox"/> Yes <input type="checkbox"/> No  |
| ❖ Public communications ( <i>approvals only</i> )   |   |
| • Office of Executive Programs (OEP) liaison has been notified of action  | <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No   |
| • Press Office notified of action (by OEP)  | <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No   |
| • Indicate what types (if any) of information dissemination are anticipated   | <input checked="" type="checkbox"/> None<br><input type="checkbox"/> HHS Press Release<br><input type="checkbox"/> FDA Talk Paper<br><input type="checkbox"/> CDER Q&As<br><input type="checkbox"/> Other |

<sup>2</sup> All questions in all sections pertain to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

|  |   |
|--|---|
| ❖ Exclusivity  |   |
| <ul style="list-style-type: none"> <li>Is approval of this application blocked by any type of exclusivity?</li> </ul>  | <input checked="" type="checkbox"/> No <input type="checkbox"/> Yes   |
| <ul style="list-style-type: none"> <li>NDA and BLAs: Is there existing orphan drug exclusivity for the “same” drug or biologic for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of “same drug” for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</i></li> </ul>  | <input checked="" type="checkbox"/> No <input type="checkbox"/> Yes<br>If, yes, NDA/BLA #      and date exclusivity expires:                          |
| <ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>  | <input type="checkbox"/> No <input type="checkbox"/> Yes<br>If yes, NDA #      and date exclusivity expires:  |
| <ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>  | <input type="checkbox"/> No <input type="checkbox"/> Yes<br>If yes, NDA #      and date exclusivity expires:  |
| <ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>   | <input type="checkbox"/> No <input type="checkbox"/> Yes<br>If yes, NDA #      and date exclusivity expires:  |
| <ul style="list-style-type: none"> <li>NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>  | <input checked="" type="checkbox"/> No <input type="checkbox"/> Yes<br>If yes, NDA #      and date 10-year limitation expires:                        |
| ❖ Patent Information (NDAs only)   |   |
| <ul style="list-style-type: none"> <li>Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.</li> </ul>  | <input checked="" type="checkbox"/> Verified<br><input type="checkbox"/> Not applicable because drug is an old antibiotic.                            |
| <ul style="list-style-type: none"> <li>Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.</li> </ul>   | 21 CFR 314.50(i)(1)(i)(A)<br><input type="checkbox"/> Verified<br>21 CFR 314.50(i)(1)<br><input type="checkbox"/> (ii) <input type="checkbox"/> (iii) |
| <ul style="list-style-type: none"> <li>[505(b)(2) applications] If the application includes a <b>paragraph III</b> certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).</li> </ul>   | <input type="checkbox"/> No paragraph III certification<br>Date patent will expire  |
| <ul style="list-style-type: none"> <li>[505(b)(2) applications] For <b>each paragraph IV</b> certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark “N/A” and skip to the next section below (Summary Reviews)).</i></li> </ul> | <input type="checkbox"/> N/A (no paragraph IV certification)<br><input type="checkbox"/> Verified   |

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

Answer the following questions for **each** paragraph IV certification:

- (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?

Yes       No

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

Yes       No

If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.

If "**No**," continue with question (3).

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes       No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes       No

If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "**No**," continue with question (5).

|   |   |
|---|---|
| <p>(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i></p> | <input type="checkbox"/> Yes <input type="checkbox"/> No  |
| <b>CONTENTS OF ACTION PACKAGE</b>   |   |
| ❖ Copy of this Action Package Checklist <sup>3</sup>  | December 3, 2009  |
| <b>Officer/Employee List</b>  |   |
| ❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list ( <i>approvals only</i> )   | <input checked="" type="checkbox"/> Included  |
| Documentation of consent/non-consent by officers/employees  | <input checked="" type="checkbox"/> Included  |
| <b>Action Letters</b>   |   |
| ❖ Copies of all action letters ( <i>including approval letter with final labeling</i> )   | Action(s) and date(s)<br>Approval - August 28, 2009<br>Complete Response –<br>November 28, 2008   |
| <b>Labeling</b>   |   |
| ❖ Package Insert ( <i>write submission/communication date at upper right of first page of PI</i> )  |   |
| <ul style="list-style-type: none"> <li>• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)</li> </ul>  |   |
| <ul style="list-style-type: none"> <li>• Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version)</li> </ul>  |   |
| <ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>  | April 30, 2008  |
| <ul style="list-style-type: none"> <li>• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable</li> </ul>   |   |
| ❖ Medication Guide/Patient Package Insert/Instructions for Use ( <i>write submission/communication date at upper right of first page of each piece</i> )  | <input type="checkbox"/> Medication Guide<br><input checked="" type="checkbox"/> Patient Package Insert<br><input type="checkbox"/> Instructions for Use<br><input type="checkbox"/> None |

<sup>3</sup> Fill in blanks with dates of reviews, letters, etc.  
Version: 8/26/09

|   |  |
|---|--|
| <ul style="list-style-type: none"> <li>Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling)</li> </ul>  |  |
| <ul style="list-style-type: none"> <li>Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version)</li> </ul>  |  |
| <ul style="list-style-type: none"> <li>Original applicant-proposed labeling</li> </ul>  |  |
| <ul style="list-style-type: none"> <li>Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable</li> </ul>   |  |
| <ul style="list-style-type: none"> <li>❖ Labels (<b>full color</b> carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>)</li> </ul>   |  |
| <ul style="list-style-type: none"> <li>Most-recent division proposal for (only if generated after latest applicant submission)</li> </ul>   |  |
| <ul style="list-style-type: none"> <li>Most recent applicant-proposed labeling</li> </ul>   |  |
| <ul style="list-style-type: none"> <li>❖ Proprietary Name <ul style="list-style-type: none"> <li>Review(s) (<i>indicate date(s)</i>)</li> <li>Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>)</li> </ul> </li> </ul>  |  |
| <ul style="list-style-type: none"> <li>❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>)</li> </ul>  | <input type="checkbox"/> RPM<br><input type="checkbox"/> DMEDP<br><input type="checkbox"/> DRISK<br><input checked="" type="checkbox"/> DDMAC 10/15/08<br><input type="checkbox"/> CSS<br><input type="checkbox"/> Other reviews |
| <b>Administrative / Regulatory Documents</b>  |  |
| <ul style="list-style-type: none"> <li>❖ Administrative Reviews (<i>e.g., RPM Filing Review<sup>4</sup>/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>)</li> </ul>  | July 3, 2008   |
| <ul style="list-style-type: none"> <li>❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>)</li> </ul>   | <input checked="" type="checkbox"/> Included   |
| <ul style="list-style-type: none"> <li>❖ Application Integrity Policy (AIP) Status and Related Documents<br/><a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a></li> </ul>     |  |
| <ul style="list-style-type: none"> <li>Applicant in on the AIP</li> </ul>   | <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No  |
| <ul style="list-style-type: none"> <li>This application is on the AIP <ul style="list-style-type: none"> <li>○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>)</li> <li>○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>)</li> </ul> </li> </ul> | <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No<br><br><input type="checkbox"/> Not an AP action   |
| <ul style="list-style-type: none"> <li>❖ Pediatric Page (<i>approvals only, must be reviewed by PERC before finalized</i>)</li> </ul>   | <input checked="" type="checkbox"/> Included   |
| <ul style="list-style-type: none"> <li>❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent (<i>include certification</i>)</li> </ul>                             | <input checked="" type="checkbox"/> Verified, statement is acceptable  |
| <ul style="list-style-type: none"> <li>❖ Outgoing communications (<i>letters (except previous action letters), emails, faxes, telecons</i>)</li> </ul>  | See action package   |
| <ul style="list-style-type: none"> <li>❖ Internal memoranda, telecons, etc.</li> </ul>  | See action package   |
| <ul style="list-style-type: none"> <li>❖ Minutes of Meetings</li> </ul>   |  |
| <ul style="list-style-type: none"> <li>PeRC (<i>indicate date of mtg; approvals only</i>)</li> </ul>  | <input type="checkbox"/> Not applicable July 22, 2008  |
| <ul style="list-style-type: none"> <li>Pre-Approval Safety Conference (<i>indicate date of mtg; approvals only</i>)</li> </ul>  | <input type="checkbox"/> Not applicable  |
| <ul style="list-style-type: none"> <li>Regulatory Briefing (<i>indicate date of mtg</i>)</li> </ul>   | <input checked="" type="checkbox"/> No mtg   |

<sup>4</sup> Filing reviews for scientific disciplines should be filed behind the respective discipline tab.  
Version: 8/26/09

|  |   |
|--|---|
| • Pre-NDA/BLA meeting ( <i>indicate date of mtg</i> )  | <input checked="" type="checkbox"/> No mtg  |
| • EOP2 meeting ( <i>indicate date of mtg</i> )   | <input checked="" type="checkbox"/> No mtg  |
| • Other (e.g., EOP2a, CMC pilot programs)  | Peds Exclusivity Board Mtg Sum<br>July 22, 2008                                       |
| ❖ Advisory Committee Meeting(s)  | <input type="checkbox"/> No AC meeting  |
| • Date(s) of Meeting(s)  |   |
| • 48-hour alert or minutes, if available ( <i>do not include transcript</i> )  |   |
| <b>Decisional and Summary Memos</b>  |   |
| ❖ Office Director Decisional Memo ( <i>indicate date for each review</i> )   | <input checked="" type="checkbox"/> None  |
| Division Director Summary Review ( <i>indicate date for each review</i> )  | <input checked="" type="checkbox"/> None  |
| Cross-Discipline Team Leader Review ( <i>indicate date for each review</i> )   | <input type="checkbox"/> None August 28, 2009   |
| PMR/PMC Development Templates ( <i>indicate total number</i> )   | <input checked="" type="checkbox"/> None  |
| <b>Clinical Information<sup>5</sup></b>  |   |
| ❖ Clinical Reviews   |   |
| • Clinical Team Leader Review(s) ( <i>indicate date for each review</i> )  |   |
| • Clinical review(s) ( <i>indicate date for each review</i> )  | August 28, 2009   |
| • Social scientist review(s) (if OTC drug) ( <i>indicate date for each review</i> )  | <input checked="" type="checkbox"/> None  |
| ❖ Safety update review(s) ( <i>indicate location/date if incorporated into another review</i> )  | August 28, 2009 clinical review   |
| ❖ Financial Disclosure reviews(s) or location/date if addressed in another review<br>OR<br>If no financial disclosure information was required, review/memo explaining why not   | November 25, 2008 clinical review   |
| ❖ Clinical reviews from other clinical areas/divisions/Centers ( <i>indicate date of each review</i> )   | <input checked="" type="checkbox"/> None  |
| ❖ Controlled Substance Staff review(s) and Scheduling Recommendation ( <i>indicate date of each review</i> )   | <input checked="" type="checkbox"/> Not needed  |
| ❖ Risk Management <ul style="list-style-type: none"> <li>• REMS Document and Supporting Statement (<i>indicate date(s) of submission(s)</i>)</li> <li>• REMS Memo (<i>indicate date</i>)</li> <li>• Review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>)</li> </ul> | <input checked="" type="checkbox"/> None  |
| ❖ DSI Clinical Inspection Review Summary(ies) ( <i>include copies of DSI letters to investigators</i> )  | <input type="checkbox"/> None requested 10/24/2008                                    |
| <b>Clinical Microbiology</b> <input type="checkbox"/> None   |   |
| ❖ Clinical Microbiology Team Leader Review(s) ( <i>indicate date for each review</i> )   | <input checked="" type="checkbox"/> None  |
| Clinical Microbiology Review(s) ( <i>indicate date for each review</i> )   | <input type="checkbox"/> None August 15, 2008<br>September 8, 2008<br>October 2, 2008 |
| <b>Biostatistics</b> <input type="checkbox"/> None   |   |
| ❖ Statistical Division Director Review(s) ( <i>indicate date for each review</i> )   | <input checked="" type="checkbox"/> None  |

<sup>5</sup> Filing reviews should be filed with the discipline reviews.  
Version: 8/26/09

|  |  |
|--|--|
| Statistical Team Leader Review(s) <i>(indicate date for each review)</i>   | <input checked="" type="checkbox"/> None   |
| Statistical Review(s) <i>(indicate date for each review)</i>   | <input type="checkbox"/> None October 20, 2008   |
| <b>Clinical Pharmacology</b> <input type="checkbox"/> None   |  |
| ❖ Clinical Pharmacology Division Director Review(s) <i>(indicate date for each review)</i>   | <input type="checkbox"/> None  |
| Clinical Pharmacology Team Leader Review(s) <i>(indicate date for each review)</i>   | <input type="checkbox"/> None  |
| Clinical Pharmacology review(s) <i>(indicate date for each review)</i>   | <input type="checkbox"/> None November 25, 2008<br>August 26, 2009<br>September 17, 2009 |
| ❖ DSI Clinical Pharmacology Inspection Review Summary <i>(include copies of DSI letters)</i>   | <input type="checkbox"/> None October 24, 2008   |
| <b>Nonclinical</b> <input type="checkbox"/> None   |  |
| ❖ Pharmacology/Toxicology Discipline Reviews   |  |
| • ADP/T Review(s) <i>(indicate date for each review)</i>   | <input checked="" type="checkbox"/> None   |
| • Supervisory Review(s) <i>(indicate date for each review)</i>   | <input checked="" type="checkbox"/> None   |
| • Pharm/tox review(s), including referenced IND reviews <i>(indicate date for each review)</i>   | <input type="checkbox"/> None November 24, 2008  |
| ❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer <i>(indicate date for each review)</i>  | <input checked="" type="checkbox"/> None   |
| ❖ Statistical review(s) of carcinogenicity studies <i>(indicate date for each review)</i>  | <input checked="" type="checkbox"/> No carc  |
| ❖ ECAC/CAC report/memo of meeting  | <input checked="" type="checkbox"/> None<br>Included in P/T review, page                 |
| ❖ DSI Nonclinical Inspection Review Summary <i>(include copies of DSI letters)</i>   | <input checked="" type="checkbox"/> None requested                                       |
| <b>Product Quality</b> <input type="checkbox"/> None   |  |
| ❖ Product Quality Discipline Reviews   |  |
| • ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>   | <input checked="" type="checkbox"/> None   |
| • Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>  | <input checked="" type="checkbox"/> None   |
| • Product quality review(s) <i>(indicate date for each review)</i>   | <input type="checkbox"/> None September 18, 2008   |
| • ONDQA Biopharmaceutics review <i>(indicate date for each review)</i>   |  |
| • BLAs only: Facility information review(s) <i>(indicate dates)</i>  | <input type="checkbox"/> None  |
| ❖ Microbiology Reviews   |  |
| • NDAs: Microbiology reviews (sterility & pyrogenicity) <i>(indicate date of each review)</i>  | <input checked="" type="checkbox"/> Not needed   |
| • BLAs: Sterility assurance, product quality microbiology <i>(indicate date of each review)</i>  |  |
| ❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i>   | <input checked="" type="checkbox"/> None   |
| ❖ Environmental Assessment (check one) (original and supplemental applications)  |  |
| <input checked="" type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i> | August 15, 2008  |
| <input type="checkbox"/> Review & FONSI <i>(indicate date of review)</i>   |  |
| <input type="checkbox"/> Review & Environmental Impact Statement <i>(indicate date of each review)</i>   |  |
| ❖ Facilities Review/Inspection   |  |

|  |  |
|--|--|
| <ul style="list-style-type: none"> <li>• NDAs: Facilities inspections (include EER printout) (<i>date completed must be within 2 years of action date</i>)</li> </ul>  | <p>Date completed: Oct.. 20, 2008</p> <input checked="" type="checkbox"/> Acceptable<br><input type="checkbox"/> Withhold recommendation   |
| <ul style="list-style-type: none"> <li>• BLAs:             <ul style="list-style-type: none"> <li>○ TBP-EER</li> <li>○ Compliance Status Check (approvals only, both original and all supplemental applications except CBEs) (<i>date completed must be within 60 days prior to AP</i>)</li> </ul> </li> </ul> | <p>Date completed:</p> <input type="checkbox"/> Acceptable<br><input type="checkbox"/> Withhold recommendation<br><p>Date completed:</p> <input type="checkbox"/> Requested<br><input type="checkbox"/> Accepted <input type="checkbox"/> Hold |
| <ul style="list-style-type: none"> <li>❖ NDAs: Methods Validation</li> </ul>   | <input checked="" type="checkbox"/> Completed<br><input type="checkbox"/> Requested<br><input type="checkbox"/> Not yet requested<br><input type="checkbox"/> Not needed   |

## Appendix A to Action Package Checklist

An NDA or NDA supplemental 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) **Or** 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.
- (3) **Or** 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) **And** 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.
- (3) **And** 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) **Or** 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.
- (3) **Or** 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 ADRA.

| Application Type/Number | Submission Type/Number | Submitter Name      | Product Name |
|-------------------------|------------------------|---------------------|--------------|
| NDA-22257               | ORIG-1                 | ROCHE PALO ALTO LLC | VALCYTE      |

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/s/

KAREN D WINESTOCK  
12/17/2009



NDA 22-257

Hoffmann-La Roche, Inc.  
Attn: Wendy L. Corbett, Ph.D., MBA  
Associate Director, Pharma Development Regulatory  
340 Kingsland Street  
Nutley, NJ 07110-1199  
Dear Dr. Corbett:

We acknowledge receipt on June 29, 2009 of your June 26, 2009 resubmission to your new drug application for VALCYTE (valganciclovir) oral solution.

We consider this a complete, class 1 response to our November 25, 2008 action letter. Therefore, the user fee goal date is August 28, 2009.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have submitted pediatric studies with this application. Once the review of this application is complete we will notify you whether you have fulfilled the pediatric study requirement for this application.

If you have any questions, call Jaewon Hong, Pharm.D., Regulatory Project Manager, at (301) 796-2013.

Sincerely,

*{See appended electronic signature page}*

Jaewon Hong, Pharm.D.  
Regulatory Health Project Manager  
Division of Antiviral Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research

-----  
**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/

-----  
Jaewon Hong  
7/10/2009 04:58:09 PM

## Attachment B: Sample PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

---

PMR/PMC Description: Perform a pharmacokinetic and safety study in pediatric heart transplant recipients < 4 months of age in order to determine appropriate dosing in this age group and submit dosing recommendations for inclusion in the package insert.

---

PMR/PMC Schedule Milestones: Final protocol Submission Date: 06/30/2010  
Study/Clinical trial Completion Date: \_\_\_\_\_  
Final Report Submission Date: 03/31/2013  
Other: Study start date 10/01/2010

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Previously, the sponsor conducted studies for the prevention of CMV disease in solid organ transplant recipients at high risk in response to the Pediatric Written Request. The Written Request specified that studies include infants and children 4 months to 16 years of age. However, about 25% of the pediatric heart transplants performed each year are performed on pediatric patients 1 month of age or younger and about half are performed during the first year of life. Because patients < 4 months of age represent a significant portion of the population for which the drug is indicated, this data is considered important. This could not be done pre-approval because data in older pediatric patients is important to determine appropriate dose ranges in the younger patients.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

To determine dosing recommendations for valganciclovir for the prevention of CMV disease in pediatric heart transplant recipients younger than 4 months of age.

3. If the study/clinical trial is a PMR, check the applicable regulation.

*If not a PMR, skip to 4.*

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?  
*Do not select the above study/clinical trial type if:* such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
*Do not select the above study/clinical trial type if:* the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
*Do not select the above study type if:* a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

|  |
|--|
| A pharmacokinetic and safety trial in pediatric heart transplant recipients < 4 months of age. |
|--|

Required

- Observational pharmacoepidemiologic study
- Registry studies

Continuation of Question 4

- Primary safety study or clinical trial
  - Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
  - Thorough Q-T clinical trial
  - Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
  - Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
  - Pharmacokinetic studies or clinical trials
  - Drug interaction or bioavailability studies or clinical trials
  - Dosing trials
  - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
- 
- Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
  - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
  - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
  - Dose-response study or clinical trial performed for effectiveness
  - Nonclinical study, not safety-related (specify)
- 
- Other  
A pharmacokinetic and safety trial in pediatric heart transplant recipients < 4 months of age.

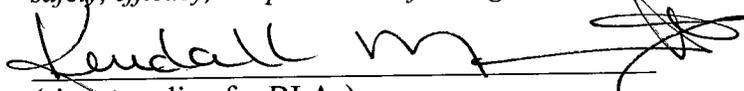
5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

---

**PMR/PMC Development Coordinator:**

*This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

  
(signature line for BLAs)

## Attachment B: Sample PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

---

PMR/PMC Description: Analyze the phenotypic nature of ganciclovir resistant viruses isolated during the clinical study CASG 109. Submit the results in a SAS transport file dataset

|                              |                                       |                   |
|------------------------------|---------------------------------------|-------------------|
| PMR/PMC Schedule Milestones: | Final protocol Submission Date:       | <u>Completed</u>  |
|                              | Study/Clinical trial Completion Date: | <u>Completed</u>  |
|                              | Final Report Submission Date:         | <u>06/30/2010</u> |
|                              | Other:                                | _____             |

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Phenotypic characterization of amino acid substitutions possibly associated with ganciclovir resistance is a labor and time intensive process that would delay availability of an effective therapy.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

Ganciclovir and valganciclovir were approved years ago when resistance analyses were not routinely required for antiviral drug development. Genotypic analysis by academic laboratories and industry has identified many possible pathways to resistance to ganciclovir. Unfortunately, the number of clinical samples for genotypic analysis is inadequate to definitively identify which of the substitutions lead to resistance. Phenotypic analysis will help to identify resistance pathways.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

***If not a PMR, skip to 4.***

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?  
***Do not select the above study/clinical trial type if:*** such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
***Do not select the above study/clinical trial type if:*** the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
***Do not select the above study type if:*** a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Introduction of identified resistance-associated substitutions into a laboratory strain by site-directed mutagenesis and assessment of the shift in susceptibility relative to the parental wild-type strain.

Required

- Observational pharmacoepidemiologic study
- Registry studies

Continuation of Question 4

- Primary safety study or clinical trial
  - Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
  - Thorough Q-T clinical trial
  - Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
  - Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
  - Pharmacokinetic studies or clinical trials
  - Drug interaction or bioavailability studies or clinical trials
  - Dosing trials
  - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
- 
- Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
  - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
  - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
  - Dose-response study or clinical trial performed for effectiveness
  - Nonclinical study, not safety-related (specify)
- 
- Other  
Phenotypic characterization of amino acid substitutions possibly associated with ganciclovir resistance
- 

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

---

**PMR/PMC Development Coordinator:**

*This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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(signature line for BLAs)

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/s/  
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JAEWON HONG  
09/16/2009

KENDALL A MARCUS  
09/16/2009

# REQUEST FOR CONSULTATION

TO (Office/Division): Sylvia Gantt, HFD-003, Rm 3549

FROM (Name, Office/Division, and Phone Number of Requestor): Althea Cuff, ONDQA, 301-796-4061

DATE  
9/16/09

IND NO.

NDA NO.  
22-2571

TYPE OF DOCUMENT  
001

DATE OF DOCUMENT  
8/31/09

NAME OF DRUG  
Valcyte

PRIORITY CONSIDERATION

CLASSIFICATION OF DRUG

DESIRED COMPLETION DATE  
12/1/09

NAME OF FIRM: Roche

## REASON FOR REQUEST

### I. GENERAL

- |   |  |  |
|---|--|--|
| <input type="checkbox"/> NEW PROTOCOL                               | <input type="checkbox"/> PRE-NDA MEETING         | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT                            | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING        |
| <input type="checkbox"/> NEW CORRESPONDENCE                         | <input type="checkbox"/> END-OF-PHASE 2 MEETING  | <input type="checkbox"/> LABELING REVISION             |
| <input type="checkbox"/> DRUG ADVERTISING                           | <input type="checkbox"/> RESUBMISSION            | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE   |
| <input type="checkbox"/> ADVERSE REACTION REPORT                    | <input type="checkbox"/> SAFETY / EFFICACY       | <input type="checkbox"/> FORMULATIVE REVIEW            |
| <input checked="" type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA               | <input type="checkbox"/> OTHER (SPECIFY BELOW):        |
| <input type="checkbox"/> MEETING PLANNED BY                         | <input type="checkbox"/> CONTROL SUPPLEMENT      |  |

### II. BIOMETRICS

- |   |   |
|---|---|
| <input type="checkbox"/> PRIORITY P NDA REVIEW  | <input type="checkbox"/> CHEMISTRY REVIEW       |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY           |
| <input type="checkbox"/> CONTROLLED STUDIES     | <input type="checkbox"/> BIOPHARMACEUTICS       |
| <input type="checkbox"/> PROTOCOL REVIEW        | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): |   |

### III. BIOPHARMACEUTICS

- |  |  |
|--|--|
| <input type="checkbox"/> DISSOLUTION             | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE  |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES         | <input type="checkbox"/> IN-VIVO WAIVER REQUEST      |

### IV. DRUG SAFETY

- |  |  |
|--|--|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL                | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE                       |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)           | <input type="checkbox"/> POISON RISK ANALYSIS                                |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP         |  |

### V. SCIENTIFIC INVESTIGATIONS

- |                                   |                                      |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS / SPECIAL INSTRUCTIONS: This supplement provides for change in Drug product microbiological specification.

This supplement is in EDR

Please review.

PDUFA Date: 01/01/2010

SIGNATURE OF REQUESTOR  
Althea Cuff

METHOD OF DELIVERY (Check one)

- DFS       EMAIL       MAIL       HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

| Application Type/Number | Submission Type/Number | Submitter Name      | Product Name |
|-------------------------|------------------------|---------------------|--------------|
| NDA-22257               | SUPPL-1                | ROCHE PALO ALTO LLC | VALCYTE      |

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/s/

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ALTHEA CUFF  
09/16/2009



NDA 21-304 SLR-007

**PRIOR APPROVAL SUPPLEMENT**

Hoffmann-La Roche Inc.  
Attn: Wendy L. Corbett, Ph.D., MBA  
Associate Director  
Pharma Development Regulatory  
340 Kingsland Street  
Nutley, NJ 07110

Dear Dr. Corbett:

We have received your supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Names of Drug Product: Valcyte® (valganciclovir hydrochloride) tablets

NDA Number: 21-304

Supplement number: SLR-007

Date of supplement: August 6, 2009

Date of receipt: August 10, 2009

This supplemental application proposes the following changes: Update the package insert (PI) and patient package insert (PPI) with revisions approved under NDA 22-257, Valcyte® (valganciclovir hydrochloride), Oral Solution.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on October 9, 2009, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be February 10, 2010.

Please cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Antiviral Products  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

If you have questions, call Sherly Abraham, R.Ph., Regulatory Project Manager, at (301)796-3198.

Sincerely,

{ See appended electronic signature page }

Victoria Tyson  
Chief, Project Management Staff  
Division of Antiviral Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research

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/s/  
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VICTORIA L Tyson  
08/26/2009



Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation ODE IV

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE:** March 13, 2009

|  |  |
|--|--|
| <b>To:</b> Wendy L. Corbett, Ph.D., MBA<br>Associate Director<br>Pharma Development Regulatory | <b>From:</b> David Araujo, PharmD<br>Regulatory Health Project Manager |
| <b>Company:</b> Hoffmann-La Roche Inc.   | Division of Antiviral Products   |
| <b>Fax number:</b> (973) 562-3700  | <b>Fax number:</b> (301)796-0669                                       |
| <b>Phone number:</b> (973) 235-8026  | <b>Phone number:</b> (301)796-9883                                     |

**Subject:** Type A Meeting Comments

**Total no. of pages including cover:** 4

**Comments:**

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**Document to be mailed:**             YES             NO

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**MEMORANDUM OF FACSIMILE CORRESPONDENCE**

**NDA:** 22-257

**Drug:** Valcyte<sup>®</sup> (valganciclovir HCl) for Oral Solution

**Date:** March 13, 2009

**Sponsor:** Hoffmann-La Roche Inc.

**From:** David Araojo, Pharm.D., Regulatory Health Project Manager, DAVP

**Through:** Debra Birnkrant, M.D., Director, Division of Antiviral Products  
C.T. Viswanathan, Ph.D., Associate Director, Division of Scientific Investigations  
Jacqueline O'Shaughnessy, Ph.D., Division of Scientific Investigations  
Kendall Marcus, M.D., Associate Director for Safety  
Andreas Piki, M.D., Medical Reviewer  
Kellie Reynolds, Pharm.D., Clinical Pharmacology Team Leader  
Vikram Arya, Ph.D., Clinical Pharmacology Reviewer  
Pravin Jadhav, Ph.D., Office of Clinical Pharmacology  
Kevin Krudys, Ph.D., Office of Clinical Pharmacology  
Karen Winestock, Chief, Project Management Staff

**Subject:** Type A Meeting Comments

---

Reference is made to your meeting request submission to NDA 22-257, dated February 11, 2009. The following comments are conveyed to you on behalf of the Division of Antiviral Products and Division of Scientific Investigations (DSI).

**Comments**

Your February 11, 2009 response to the January 26, 2009 DSI request for additional information adequately addresses the issues raised with the following exceptions:

- Contrary to your claim, there is no basis to accept the subject sample concentrations from run GAN041216a (Study WV16726) in that the QCs failed to meet the run acceptance criteria. Use of ISR data and application of calibration curves from different runs are not acceptable approaches to assure the accuracy of a failed run elsewhere. In this regard, the PK evaluation for Study WV16726 should be repeated after excluding the subject sample data from the failed run.
- For all runs across the studies, your response provided summary tables of back-calculated calibration standard results after automatic reintegration of the chromatograms, with failing or excluded standards in red text (Attachment 2). To address item 4 from the January 26, 2009 DSI

request, please provide similar summary tables for the QC results for all study runs in the three studies. Attachment 4 of your response only provided QC data for the failed run GAN041216a and run GAN041216b in Study WV16726.

**Meeting Question Comments** (FDA response to questions listed in bold.)

**1. Storage Stability Data**

In the January 26, 2009 FDA Fax, DSI commented that the storage stability concern has been satisfactorily addressed. As stated in the November 25, 2008 Complete Response Letter for NDA 22-257, Roche understands that all approvability issues relating to the frozen stability data that cover the duration of storage are now resolved. Does the Agency agree?

**The storage stability concern has been satisfactorily addressed.**

**2. Identify a Set of Integration Parameters and Re-integrate All Chromatograms**

a) Roche identified a set of integration parameters for each run in studies WV16726 and CASG109 and re-integrated all chromatograms in a consistent manner. Does the Agency agree that the integration parameters and the re-integrated results of all chromatograms for studies WV16726 and CASG109 provided in the submissions listed above adequately address the integration observations noted on the Form 483 issued by DSI during their analytical inspection at (b) (4)

b) Roche compared the sample concentration data from the original manually integrated chromatograms and the automatic re-integrated chromatograms, and provided the result of comparisons in the November 25, 2008 and December 23, 2008 submissions. The overall differences in the concentration data between the manual and automatic integration methods were found to be less than 1% (mean difference <1% in each study). Roche believes that this small difference will not change the study conclusions. Does the Agency agree?

**Automatic reintegration of the chromatograms in a consistent manner within each run addresses the inspectional finding regarding inconsistent integration of chromatograms involving manual integrations.**

**3. Repeat of PK and/or PD Evaluations in Studies WV16726 and CASG109**

a) Because the mean difference between the manually integrated data and the automatic re-integrated data is <1% in each study, Roche believes the PK/PD evaluations using the original manually integrated data vs. the automated integrated data will be similar (please refer to Appendix 3), and that repeating the PK/PD evaluations for studies WV16726 and CASG109 are not necessary. Does the Agency agree with Roche's position?

**Your claim that recalculation of the PK and/or PD evaluations is not necessary as the mean difference between the manual and reintegrated results is <1% is not relevant in the context of a failing run that was not rejected. Please note that consistent integration of samples within a run is needed to assure data accuracy. In this regard, the PK and/or PD evaluations for these studies should be recalculated using the concentration results obtained following automatic reintegration of the chromatograms.**

**Although study conclusions are unlikely to change, a PK evaluation is required for confirmation. Also, the PK results presented in the label should reflect the final, acceptable dataset. To address these concerns, please perform the following:**

- **Re-run the final population pharmacokinetic models from studies WV16726 and CASG109 using the automatic re-integration data and excluding the data from run GAN041216a from study WV16726.**
- **Provide tables with a comparison of the population pharmacokinetic parameter estimates from studies WV16726 and CASG109 using the datasets from the original submission and the updated datasets.**
- **Provide spreadsheets with individual pharmacokinetic parameter estimates for all subjects from studies WV16726 and CASG109 using the datasets from the original submission and the updated datasets.**
- **Update sections 8.4 and 12.3 (Table 10) of the label to reflect the pharmacokinetic results using the updated datasets.**

b) If the Agency will not accept the original PK/PD evaluations using manual integrated data and wants the PK/PD evaluations recalculated using the automated integration data, will the Agency consider a path forward with a proposal to bring Valcyte for Oral Solution to market while any required repeat PK/PD evaluations are completed as post-marketing commitments?

**The Division will have to review the re-analysis (to be conducted as outlined in response to question #3a) prior to taking any regulatory action on a resubmitted NDA.**

#### 4. Other

Does the Agency have any other significant labeling comments not yet communicated to the Sponsor based on the NDA review?

**No significant labeling comments.**

We are providing the above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me if you have any questions regarding the contents of this transmission at 301-796-0669.

---

David Araojo, Pharm.D.  
Regulatory Health Project Manager  
Division of Antiviral Products

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/s/

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David Araojo  
3/13/2009 03:07:39 PM  
CSO

Kendall Marcus  
3/13/2009 03:10:23 PM  
MEDICAL OFFICER



Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation ODE IV

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE:** January 26, 2009

|  |  |
|--|--|
| <b>To:</b> Snehal Shah, Pharm.D.<br>Program Manager<br>Pharma Development Regulatory | <b>From:</b> David Araujo, PharmD<br>Regulatory Health Project Manager |
| <b>Company:</b> Hoffmann-La Roche Inc.   | Division of Antiviral Products   |
| <b>Fax number:</b> (973) 562-3700  | <b>Fax number:</b> (301)796-0669                                       |
| <b>Phone number:</b> (973) 235-5313  | <b>Phone number:</b> (301)796-9883                                     |
| <b>Subject:</b> DSI Comments   |  |

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**Total no. of pages including cover:** 3

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**Comments:**

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**MEMORANDUM OF FACSIMILE CORRESPONDENCE**

**NDA:** 22-257

**Drug:** Valcyte® (valganciclovir HCl) for Oral Solution

**Date:** January 26, 2009

**Sponsor:** Hoffmann-La Roche Inc.

**From:** David Araojo, Pharm.D., Regulatory Health Project Manager, DAVP

**Through:** Debra Birnkrant, M.D., Director, Division of Antiviral Products  
C.T. Viswanathan, Ph.D., Associate Director, Division of Scientific Investigations  
Jacqueline O’Shaughnessy, Ph.D., Division of Scientific Investigations

**Subject:** DSI Comments

---

Reference is made to your submission to NDA 22-257, dated December 23, 2008. The following comments are conveyed to you on behalf of the Division of Scientific Investigations (DSI).

**DSI**

With respect to your response dated December 23, 2008, please address the following issues:

1. As described in your response, run GAN041216a in study WV16726 failed to meet the QC acceptance criteria following automatic re-integration in that 4 of 8 QCs failed. As the results of failed runs cannot be accepted, please provide a list of the subject samples (patient, sample number, sample time, sample date) assayed in the aforementioned run.
2. For all three studies (WV16726, WP16302, CASG109), audit trails for the automatic re-integrations (extension “FDA”) documented that some calibration standards were not used. For example, in Study WP16302 standard 5 was not used in many runs. Various reasons were documented in the audit trail for not using certain calibration standards (e.g., reject outlier, inactivate, deactivate, remove duplicate standard). In contrast, Table 5 (Accuracy of back-calculated calibration samples using automated integration) in the (b) (4) response dated November 25, 2008 only flagged one calibration standard across Study WP16302 as having an unacceptable value (run GAN051123, 0.04 µg/ml). For all three studies, please identify all calibration standards that were excluded from the calibration response, describe the basis for the exclusion, and address any impact on run acceptance/rejection.

3. In studies CASG109 and WV16726, audit trails for the automatic re-integration (extension “FDA”) documented that concentrations of the calibration standards and QCs were changed in several runs. As examples, run GAN050217 in study CASG109 and run GAN050318a in study WV16726. For all three studies, please identify all runs in which calibration standard and QC concentrations were changed, provide the basis for the change, and address any impact on run acceptance/rejection.
4. In addressing items 2 and 3 above, please provide QC and calibration tables for the automatic re-integrations that identify the failing results.
5. Several QC chromatograms display interference on the tail end of the analyte peak. As an example, run GAN050623 in study CASG109. Please address the extent to which this interference impacts the accurate quantitation of ganciclovir in the subject samples across all three studies.
6. Please explain the basis for the withdrawal of the submission dated December 15, 2008.
7. The storage stability concern has been satisfactorily addressed.

We are providing the above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me if you have any questions regarding the contents of this transmission at 301-796-0669.

---

David Araojo, Pharm.D.  
Regulatory Health Project Manager  
Division of Antiviral Products

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/s/

-----  
David Araojo  
1/26/2009 01:03:15 PM  
CSO

Debra Birnkrant  
1/27/2009 05:09:16 PM  
MEDICAL OFFICER  
NDA 22-257

**MEMORANDUM**

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

**DATE:** November 21, 2008

**TO:** HFD-530: Division File

**FROM:** David Araojo, Regulatory Project Manager

**SUBJECT:** **Administrative Split of NDA 22-257 dated April 30, 2008**

**DFS To:** NDA 22-257 N-000 and [REDACTED] (b) (4)

Please refer to new drug application dated April 30, 2008, received May 1, 2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Valcyte® (valganciclovir hydrochloride) for oral solution. This new drug application provides for the use of Valcyte® (valganciclovir hydrochloride) for oral solution for prevention of cytomegalovirus disease in pediatric kidney and heart transplant patients at high risk, [REDACTED] (b) (4)

[REDACTED] (b) (4)

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/s/

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David Araojo  
11/21/2008 01:06:12 PM  
CSO

## RECORD OF FDA TELECONFERENCE

**Date of Meeting:** October 31, 2008

**NDA:** 22-257

**Drug:** Valcyte (valganciclovir HCl) for oral solution

**Sponsor:** Roche

**Subject:** Discuss NDA administrative split and DSI result

### Division of Antiviral Products (DAVP) Participants:

Debra Birnkrant, Division Director  
Kendall Marcus, Associate Director for Safety  
Andreas Pikis, Medical Reviewer  
Kellie Reynolds, Clinical Pharmacology Team Leader  
Vikram Arya, Clinical Pharmacology Reviewer  
Karen Winestock, Chief Project Management Staff  
David Araojo, Project Manager

### Roche Participants:

Snehal Shah, Regulatory Affairs  
Ellen Carey, Regulatory Affairs  
Lisa Luther, Regulatory Affairs  
Debbie Marcantuono, Regulatory Affairs  
Peter Cooksey, Clinical Operations  
Paul Oxley, Clinical Operations  
Bonnie Brennan, Clinical Pharmacologist  
Zuzana Lindberg, Life Cycle Team Leader

### Background

This teleconference was held at the request of DAVP to discuss Roche's NDA 22-257. A review by the Division of Scientific Investigation (DSI) dated October 24, 2008, noted that for Study WP 16302, the pivotal bioequivalence study, the clinical site failed to retain the reserve samples as required by 21 CFR 320.38. In addition, the unused drugs were returned to the Sponsor. The retention of the reserve samples is critical for assuring the authenticity of the test and reference products used in the pivotal bioequivalence trial. Therefore, the data from study WP16302 cannot be used (b) (4)

(b) (4)

**Discussion Points**

1. The inspection of the analytical site in the (b) (4) is pending and expected to be completed in the next two weeks. The site inspection is needed to support the pediatric indication for Valcyte oral solution.
2. The data from the pivotal bioequivalence study (WP 16302) cannot be confirmed because the clinical site did not retain the samples from the study. Therefore, the data cannot be used (b) (4)  
(b) (4)
3. As a result, the NDA will be administratively split into two NDAs; (b) (4)  
(b) (4) Roche will submit a (b) (4)  
revised label for the pediatric indication, (b) (4)  
(b) (4)

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/s/

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David Araojo  
11/6/2008 01:14:35 PM  
CSO

Debra Birnkrant  
11/6/2008 04:14:57 PM  
MEDICAL OFFICER  
NDA 22-257



Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation ODE IV

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE:** October 28, 2008

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| <b>To:</b> Snehal Shah, Pharm.D.<br>Program Manager<br>Pharma Development Regulatory | <b>From:</b> David Araujo, PharmD<br>Regulatory Health Project Manager |
| <b>Company:</b> Hoffmann-La Roche Inc.   | Division of Antiviral Products   |
| <b>Fax number:</b> (973) 562-3700  | <b>Fax number:</b> (301)796-0669                                       |
| <b>Phone number:</b> (973) 235-5313  | <b>Phone number:</b> (301)796-9883                                     |
| <b>Subject:</b> Chemistry Comments   |  |

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**Total no. of pages including cover:** 3

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**Comments:**

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**MEMORANDUM OF FACSIMILE CORRESPONDENCE**

**NDA:** 22-257

**Drug:** Valcyte® (valganciclovir HCl) for Oral Solution

**Date:** October 28, 2008

**Sponsor:** Hoffmann-La Roche Inc.

**From:** David Araujo, Pharm.D., Regulatory Health Project Manager

**Through:** Norman Schmuff, Ph.D., Branch Chief, ONDQA  
Ted Chang, Ph.D., Chemistry Reviewer, ONDQA

**Subject:** Chemistry Comments

---

Reference is made to your NDA 22-257, dated April 30, 2008. The following comments are conveyed to you on behalf of the chemistry review team.

**Chemistry**

- Labeling Review: Remove the word (b) (4) from the drug product name on the labels and package insert. In other words, change the name from (b) (4) to (b) (4) to “Valcyte (valganciclovir hydrochloride) for oral solution”.
- SPL Review:
  1. Change the drug product name to be the same/consistent with the PI and labels.
  2. In the DLDE section:
    - a. Change the drug product name to be the same/consistent with the PI and labels.
    - b. List each ingredient in a separate line.
    - c. Please explain what is meant by “Multilevel Packaging,” and how you chose between listing the content in terms of milliliters versus grams.

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David Araojo, Pharm.D.  
Regulatory Health Project Manager  
Division of Antiviral Products

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/s/

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David Araojo  
10/28/2008 10:00:36 AM  
CSO

Norman Schmuff  
10/28/2008 11:24:52 AM  
CHEMIST



Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation ODE IV

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE: September 9, 2008**

|   |  |
|---|--|
| <b>To: Snehal Shah, Pharm.D.</b><br>Program Manager<br><b>Pharma Development Regulatory</b> | <b>From: Monica Zeballos, Pharm.D., for David Araojo, Pharm.D.</b><br>Regulatory Project Manager |
| <b>Company: Hoffmann-La Roche Inc.</b>  | Division of Antiviral Products   |
| <b>Fax number: (973) 562-3700</b>   | <b>Fax number: (301)796-0840</b>   |
| <b>Phone number: (973) 235-5313</b>   | <b>Phone number: (301)796-9883</b>   |

**Subject: Microbiology Comments**

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**Total no. of pages including cover: 3**

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**Comments: Dr. Shah, please confirm receipt of this fax by emailing me at**  
**monica.zeballos@fda.hhs.gov**

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**MEMORANDUM OF FACSIMILE CORRESPONDENCE**

**NDA:** 22-257

**Drug:** Valcyte<sup>®</sup> (valganciclovir HCl) Powder for Oral Solution

**Date:** September 9, 2008

**Applicant:** Hoffmann-La Roche Inc.

**From:** Monica Zeballos, Pharm.D., for David Araujo, Pharm.D., Regulatory Project Manager, Division of Antiviral Products (DAVP)

**Through:** Nilambar Biswal, Ph.D., Microbiology Reviewer, DAVP  
Jules O'Rear, Ph.D., Microbiology Team Leader, DAVP  
Scott Proestel, M.D., Acting Medical Team Leader, DAVP

**Subject:** Microbiology Comments

---

Reference is made to your NDA 22-257, dated April 30, 2008. The following comments are conveyed to you on behalf of the microbiology review team and are in response to your submission dated August 15, 2008.

1. Please provide a description of the experimental protocol, results and interpretation of the results presented in Figure 1 (a, b and c). Please include a description of the legends for this Figure, and define the "lower limit detection of CMV viral load." In addition, please explain whether the solid line at  $2 \log_{10}$  viral load in these figures represents the lower limit of quantification or detection of CMV DNA.
2. In response to an earlier request (on February 13, 2002, IND 63,389 SN 001), the sponsor of the Clinical Trial CASG 109 (Division of Microbiology and Infectious Diseases, NIAID, NIH) had committed to use more recent and advanced PCR methodology sensitive enough to detect  $<10$  copies/5  $\mu$ l of CMV DNA, or even "a single copy of CMV-DNA-containing plasmid in most of the assays." Please explain why the current experiments were designed to set the limit of detection of CMV load to about  $2 \log_{10}$  (Figures 1a and 1b).
3. Please explain why a concentration  $\geq 10^4$  copies/ml of CMV DNA (as the limit of detection, second sentence, last paragraph, page 6 of 17 of this submission) was needed for genotypic assay, especially since the sponsor of the Clinical Trial CASG 109 had committed to use more recent and advanced PCR methodology to detect  $<10$  copies/5  $\mu$ l of CMV DNA or even "a single copy of CMV DNA."

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Monica Zeballos, Pharm.D., for David Araojo, Pharm.D.  
Regulatory Project Manager  
Division of Antiviral Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research

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/s/

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Monica Zeballos  
9/15/2008 07:35:56 AM  
CSO

## Araojo, David

---

**From:** Araojo, David  
**Sent:** Thursday, July 24, 2008 9:34 AM  
**To:** 'Shah, Snehal'  
**Subject:** Valcyte Pediatric Exclusivity

Dr. Snehal Shah,

Pediatric Exclusivity has been granted for studies conducted on Valcyte (valganciclovir), effective July 24, 2008, under section 505A of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355a), as amended by the Best Pharmaceuticals for Children Act (BPCA). This information will be reflected on CDER's pediatric web site and in the monthly update of the Orange Book. For additional information, please see the "Guidance for Industry - Qualifying for Pediatric Exclusivity Under Section 505A of the Federal Food, Drug, and Cosmetic Act." <http://www.fda.gov/cder/guidance/2891fnl.pdf>

In accordance with section 505A(e)(1) of the Act, as amended by FDAAA (Pub. L. No. 110-85), approved drugs for which a pediatric exclusivity determination was made, on or after September 27, 2007, shall have a copy of the Written Request and any amendments posted on CDER's pediatric web site.

In addition, we remind you that section 17 of the BPCA, as reauthorized and amended under the FDA Amendments Act of 2007, requires for one year after pediatric labeling is approved, any report received by FDA of an adverse event associated with the drug granted exclusivity will be referred to the Office of Pediatric Therapeutics. This process occurs for all products granted Pediatric Exclusivity regardless of the regulatory action taken. The Director of that Office will provide for a review of the adverse event reports by the Pediatric Advisory Committee (PAC) and will obtain recommendations from that Committee on action FDA should take.

Regards,  
David

\*\*\*\*\*

*David E. Araojo, Pharm.D.  
LCDR, USPHS  
Regulatory Health Project Manager  
Division of Antiviral Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research, FDA  
Ph: (301) 796-0669  
Fax: (301) 796-9883  
Email: david.araojo@fda.hhs.gov*

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/s/

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David Araojo  
7/24/2008 09:46:59 AM  
CSO

## REQUEST FOR CONSULTATION

TO (Office/Division): **Tammie Brent-Steele, Maternal Health Team/OND**

FROM (Name, Office/Division, and Phone Number of Requestor): **David Araojo, RPM, DAVP  
301-796-0669**

DATE  
**9/22/2008**

IND NO.

NDA NO.  
**22-257**

TYPE OF DOCUMENT  
**BL**

DATE OF DOCUMENT  
**7/11/2008**

NAME OF DRUG  
**Valcyte**

PRIORITY CONSIDERATION

CLASSIFICATION OF DRUG

DESIRED COMPLETION DATE  
**10/13/2008**

NAME OF FIRM: **Roche**

### REASON FOR REQUEST

#### I. GENERAL

- |  |  |  |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL                    | <input type="checkbox"/> PRE-NDA MEETING         | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER     |
| <input type="checkbox"/> PROGRESS REPORT                 | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING            |
| <input type="checkbox"/> NEW CORRESPONDENCE              | <input type="checkbox"/> END-OF-PHASE 2 MEETING  | <input type="checkbox"/> LABELING REVISION                 |
| <input type="checkbox"/> DRUG ADVERTISING                | <input type="checkbox"/> RESUBMISSION            | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE       |
| <input type="checkbox"/> ADVERSE REACTION REPORT         | <input type="checkbox"/> SAFETY / EFFICACY       | <input type="checkbox"/> FORMULATIVE REVIEW                |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA               | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY              | <input type="checkbox"/> CONTROL SUPPLEMENT      |  |

#### II. BIOMETRICS

- |   |   |
|---|---|
| <input type="checkbox"/> PRIORITY P NDA REVIEW  | <input type="checkbox"/> CHEMISTRY REVIEW       |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY           |
| <input type="checkbox"/> CONTROLLED STUDIES     | <input type="checkbox"/> BIOPHARMACEUTICS       |
| <input type="checkbox"/> PROTOCOL REVIEW        | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): |   |

#### III. BIOPHARMACEUTICS

- |  |  |
|--|--|
| <input type="checkbox"/> DISSOLUTION             | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE  |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES         | <input type="checkbox"/> IN-VIVO WAIVER REQUEST      |

#### IV. DRUG SAFETY

- |  |  |
|--|--|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL                | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE                       |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)           | <input type="checkbox"/> POISON RISK ANALYSIS                                |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP         |  |

#### V. SCIENTIFIC INVESTIGATIONS

- |                                   |                                      |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS / SPECIAL INSTRUCTIONS: Please review and comment on label sections 8.1 and 8.3. The proposed label can be found in the EDR: \\FDSWA150\NONECTD\N22257\N\_000\2008-07-11A. Thank you!

SIGNATURE OF REQUESTOR  
**David Araojo**

METHOD OF DELIVERY (Check one)  
 DFS     EMAIL     MAIL     HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/

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David Araojo  
9/22/2008 11:24:33 AM



**Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation ODE IV**

**FACSIMILE TRANSMITTAL SHEET**

**DATE: July 1, 2008**

|  |  |
|--|--|
| <b>To:</b> Snehal Shah, Pharm.D.<br>Program Manager<br>Pharma Development Regulatory | <b>From:</b> David Araujo, PharmD<br>Regulatory Health Project Manager |
| <b>Company:</b> Hoffmann-La Roche Inc.   | Division of Antiviral Products   |
| <b>Fax number:</b> (973) 562-3700  | <b>Fax number:</b> (301)796-0669                                       |
| <b>Phone number:</b> (973) 235-5313  | <b>Phone number:</b> (301)796-9883                                     |
| <b>Subject:</b> PLR Label Format comments  |  |

**Total no. of pages including cover: 3**

**Comments:**

**Document to be mailed:**             YES             NO

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



**MEMORANDUM OF FACSIMILE CORRESPONDENCE**

**NDA:** 22-257  
**Drug:** Valcyte<sup>®</sup> (valganciclovir HCl) Powder for Oral Solution  
**Date:** July 1, 2008  
**Sponsor:** Hoffmann-La Roche Inc.  
**From:** David Araojo, Pharm.D., Regulatory Health Project Manager  
**Subject:** Label Format Comments

---

Reference is made to your NDA 22-257, dated April 30, 2008.

Please see the following annotated pages representing the labeling format comments we have at this time. This facsimile will also be sent via electronic mail for ease of distribution and review of annotated changes. Please submit a revised, clean word copy of the labels within 14 days. At this time, an official submission in SPL is not required, as other changes to the label content may occur during review of the NDA.

We are providing the above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me if you have any questions regarding the contents of this transmission.

---

David Araojo, Pharm.D.  
Regulatory Health Project Manager  
Division of Antiviral Products

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/s/

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David Araojo  
7/1/2008 01:28:04 PM  
CSO



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

**FILING COMMUNICATION**

NDA 22-257

Hoffmann-La Roche Inc.  
Attn: Snehal Shah, Pharm.D.  
Program Manager, Pharma Development Regulatory  
340 Kingsland Street  
Nutley, NJ 07110-1199

Dear Dr. Shah:

Please refer to your new drug application (NDA) dated April 30, 2008, received May 1, 2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Valcyte<sup>®</sup> (valganciclovir hydrochloride) Powder for Oral Solution.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Priority**. Therefore, the user fee goal date is November 1, 2008.

During our filing review of your application, we identified the need for additional information:

**Clinical**

1. Within 10 days, please submit a revised dataset that incorporates toxicity grade scoring for laboratory abnormalities for all protocols.

**Microbiology**

2. Please provide the raw data on the exact viral load (as measured by PCR) in each patient at various time points during the treatment and follow-up periods in Study CASG 109. Please submit the data electronically in spreadsheet format as SAS transport files.
3. Please submit a supplemental study report with the genotypic and phenotypic data obtained in CASG 109 as SAS transport files as soon as both sets of data are available. Please provide a definitive time frame for the submission of these data, so that we can complete our review of NDA 22-257 in a timely manner.

Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

If you have not already done so, you must submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/oc/datacouncil/spl.html>. The content of labeling must be in the Prescribing Information (physician labeling rule) format.

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have submitted pediatric studies with this application for pediatric patients, ranging from neonates to 16 years of age. Once the review of this application is complete we will notify you whether you have fulfilled the pediatric study requirement for this application.

If you have any questions, call David Araujo, Pharm.D., Regulatory Project Manager, at (301) 796-0669.

Sincerely,

*{See appended electronic signature page}*

Debra Birnkrant, M.D.  
Director  
Division of Antiviral Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research

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/s/

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Jeffrey Murray

6/30/2008 03:30:25 PM

**DSI CONSULT**

**Request for Biopharmaceutical Inspections**

**DATE:** June 20, 2008

**TO:** Associate Director for Bioequivalence  
Division of Scientific Investigations, HFD-48

**THROUGH:** John Lazor  
Director, Division of Clinical Pharmacology 4

**FROM:** David Araujo, Regulatory Project Manager, HFD-530

**SUBJECT:** **Request for Biopharmaceutical Inspections**  
NDA 22-257  
Valcyte (valganciclovir HCl) Powder for Oral Solution

**Study/Site Identification:**

As discussed with you, the following studies/sites pivotal to approval (OR, raise question regarding the quality or integrity of the data submitted and) have been identified for inspection:

| Study #  | Clinical Site (name, address, phone, fax, contact person, if available) | Analytical Site (name, address, phone, fax, contact person, if available) |
|----------|---|---|
| WP 16302 | See attached  | (b) (4)<br>[Redacted]   |
| WV 16726 | See attached  | (b) (4)<br>[Redacted]   |

|          |  |         |
|----------|--|---------|
|          |  | (b) (4) |
| CASG 109 | UT Southwestern Medical Center<br>Department of Pediatrics<br>5323 Harry Hines Blvd.<br>Dallas, TX 75390-9063<br><br>Principal Investigator: Pablo Sanchez,<br>MD<br>Phone: 214-648-3753<br>Fax: 214-648-2481<br><br>(b) (4) | (b) (4) |

**International Inspections:**

**(Please note: International inspections require sign-off by the ORM Division Director or DPE Division Director.)**

We have requested an international inspection because:

There is a lack of domestic data that solely supports approval;

X  Other (please explain): The studies are pivotal for relative bioavailability.

**Goal Date for Completion:**

We request that the inspections be conducted and the Inspection Summary Results be provided by **September 30, 2008**. We intend to issue an action letter on this application by **October 31, 2008**.

Should you require any additional information, please contact David Araojo.

Concurrence:

Kellie Reynolds, Clinical Pharmacology Team Leader  
Vikram Arya, Clinical Pharmacology Reviewer

**5 Pages has been Withheld in Full immediately following this page as B4**

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/s/

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John Lazor  
6/20/2008 04:23:31 PM

# DSI CONSULT: Request for Clinical Inspections

**Date:** June 2, 2008

**To:** Constance Lewin, M.D., M.P.H, Branch Chief, GCP1, HFD-46  
Joe Salewski., Branch Chief (Acting), GCP2, HFD-47

**Through:** Kendall Marcus, MD, Medical Team Leader, DAVP  
Andreas Pikis, MD, Medical Reviewer, DAVP

**From:** David Araojo, Regulatory Health Project Manager/DAVP/HFD-530

**Subject:** **Request for Clinical Site Inspections**

## **I. General Information**

Application#: NDA 22-257

Sponsor/Sponsor contact information (to include phone/email):

Contact: Roche  
Snehal Shah, PharmD  
973-235-5313  
snehal.shah@roche.com

Drug: Valcyte (valganciclovir HCl) Powder for Oral Solution

NME: No

Standard or Priority: Priority

Study Population < <sup>(b)</sup><sub>(4)</sub> years of age: Yes

Pediatric exclusivity: TBD

PDUFA: November 1, 2008

Action Goal Date: October 31, 2008

Inspection Summary Goal Date: October 15, 2008

## **II. Background Information**

Valcyte 450 mg Tablets are approved in the US for the treatment of CMV retinitis in patients with AIDS, and for the prevention of CMV disease in kidney, heart, and kidney-pancreas transplant patients at high risk. (b) (4)

This original new drug application requests approval of a new formulation of Valcyte, the 50 mg/mL powder for oral solution, that would allow for flexible dosing for the same indications.

**III. Protocol/Site Identification**

*Include the Protocol Title/# for all protocols to be audited. Complete the following table.*

| Site # (Name,Address, Phone number, email, fax#)   | Protocol #              | Number of Subjects | Indication |
|--|-------------------------|--------------------|------------|
| Dr. Pablo Sanchez<br>UT Southwestern Medical Center<br>Department of Pediatrics<br>5323 Harry Hines Blvd.<br>Dallas, TX 75390-9063 | DMID 01-595/<br>CASG109 | 9                  |            |
| Dr. Robert Ettenger<br>UCLA Medical Center<br>10833 Le Conte Ave<br>Los Angeles, CA 90095  | WV16726                 | 5                  |            |
| Dr. S. Paul Hmiel<br>Washington University<br>School of Medicine<br>660 S. Euclid Ave.<br>St. Louis, MO 63110                      | WV16726                 | 5                  |            |

**IV. Site Selection/Rationale**

Standard Inspection request

**Domestic Inspections:**

Reasons for inspections (please check all that apply):

- Enrollment of large numbers of study subjects
- High treatment responders (specify):
- Significant primary efficacy results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
- Other (specify):

**International Inspections:** N/A

Reasons for inspections (please check all that apply):

- There are insufficient domestic data
- Only foreign data are submitted to support an application
- Domestic and foreign data show conflicting results pertinent to decision-making

Page 3-Request for Clinical Inspections

\_\_\_\_\_ There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.

\_\_\_\_\_ Other (specify) (Examples include: Enrollment of large numbers of study subjects and site specific protocol violations. This would be the first approval of this new drug and most of the limited experience with this drug has been at foreign sites, it would be desirable to include one foreign site in the DSI inspections to verify the quality of conduct of the study).

Should you require any additional information, please contact David Araujo at Ph: 301-796-0669 or Andreas Pikis at Ph: 301-796-0787.

Concurrence: (as needed)

\_\_\_\_\_Kendall Marcus\_\_\_\_\_ Medical Team Leader  
\_\_\_\_\_ Medical Reviewer  
\_\_\_\_\_ Director, Division Director (for foreign inspection requests only)

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/s/

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David Araojo  
6/2/2008 03:13:21 PM



Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation ODE IV

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE:** May 16, 2008

|   |  |
|---|--|
| <b>To:</b> Wendy Corbett, Ph.D., MBA<br>Senior Program Manager<br>Pharma Development Regulatory | <b>From:</b> David Araojo, PharmD<br>Regulatory Health Project Manager |
| <b>Company:</b> Hoffmann-La Roche Inc.  | Division of Antiviral Products   |
| <b>Fax number:</b> (973) 562-3700   | <b>Fax number:</b> (301)796-0669                                       |
| <b>Phone number:</b> (973) 235-8026   | <b>Phone number:</b> (301)796-9883                                     |
| <b>Subject:</b> Chemistry Comments  |  |

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**Total no. of pages including cover:** 3

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**Comments:**

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**Document to be mailed:**             YES             NO

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**MEMORANDUM OF FACSIMILE CORRESPONDENCE**

**NDA:** 22-257

**Drug:** Valcyte<sup>®</sup> (valganciclovir HCl) Powder for Oral Solution

**Date:** May 16, 2008

**Sponsor:** Hoffmann-La Roche Inc.

**From:** David Araujo, Pharm.D., Regulatory Health Project Manager

**Through:** Norman Schmuff, Ph.D., Branch Chief, ONDQA  
Ted Chang, Ph.D., Chemistry Reviewer, ONDQA

**Subject:** Chemistry Comments

---

Reference is made to your NDA 22-257, dated April 30, 2008. The following comments are conveyed to you on behalf of the chemistry review team.

**Chemistry**

**Regarding Valganciclovir HCl Drug Substance:**

We note the statement in the file substan.pdf:

The approved supplier of the valganciclovir hydrochloride is:  
Roche Colorado Corporation  
2075 North 55<sup>th</sup> Street  
Boulder, Colorado

We assume this is the drug substance manufacturing site. Please confirm this assumption and supply the CFN/FEI number and contact information.

Also, please provide a list, including contact information, FEIs, etc, of the other facilities where valganciclovir HCl drug substance is manufactured and tested. This information is needed to plan for inspections for NDA 22-257. Please also provide an overview of any significant changes made to the drug substance since the original approval of NDA 21-304.

**Regarding Valcyte<sup>®</sup> Powder for Oral Solution:**

Please provide contact information (name, phone) for the drug product manufacturing and testing sites, or a reference to the location if this information is contained in the NDA submission.

We are providing the above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me if you have any questions regarding the contents of this transmission.

---

David Araojo, Pharm.D.  
Regulatory Health Project Manager  
Division of Antiviral Products

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/s/

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David Araojo  
5/16/2008 01:21:12 PM  
CSO

Norman Schmuff  
5/18/2008 11:13:44 AM  
CHEMIST



NDA 22-257

**NDA ACKNOWLEDGMENT**

Roche Palo Alto LLC  
c/o Hoffmann-La Roche Inc.  
Attention: Wendy Corbett, Ph.D., MBA  
340 Kingsland Street  
Nutley, NJ 07110-1199

Dear Dr. Corbett:

We have received your new drug application (NDA) submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Valcyte™ (valganciclovir hydrochloride) –Powder for Oral Solution  
50 mg/mL

Date of Application: April 30, 2008

Date of Receipt: May 1, 2008

Our Reference Number: NDA 22-257

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on June 30, 2008 in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/oc/datacouncil/spl.html>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must be in the Prescribing Information (physician labeling rule) format.

The NDA number provided above must be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Antiviral Products  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/cder/ddms/binders.htm>.

If you have any questions, call David Araujo, Pharm.D., Regulatory Project Manager, at (301) 796-0669.

Sincerely,

*{See appended electronic signature page}*

Paras Patel, R.Ph.  
Acting Chief, Project Management Staff  
Division of Antiviral Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research

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/s/

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Paras Patel  
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