

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**021246Orig1s045 and 021087Orig1s062**

**ADMINISTRATIVE and CORRESPONDENCE  
DOCUMENTS**

## EXCLUSIVITY SUMMARY

NDA # 21087 and 21246

SUPPL # 062 and 045

HFD # 530 (DAVP)

Trade Name TAMIFLU

Generic Name oseltamivir phosphate

Applicant Name Hoffmann-La Roche, Inc.

Approval Date, If Known

### 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

SE5: New Patient Population

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.

N/A

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:

N/A

d) Did the applicant request exclusivity?

YES  NO

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

N/A

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?

No

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# 21087

Tamiflu (oseltamivir phosphate) 30, 45, 75 mg capsules

NDA# 21246

Tamiflu (oseltamivir phosphate) 6 mg/mL oral suspension

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:

N/A

(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:

N/A

(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:

N/A

(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:

- Investigation #1 CASG 114 (WP20749): "A Pharmacokinetic/Pharmacodynamic and Safety Evaluation of Oseltamivir (Tamiflu) for the Treatment of Children Less Than 24 Months of Age with Confirmed Influenza Infection."
- Investigation #2 WP22849: "An Open Label, Prospective, Pharmacokinetic/Pharmacodynamic, and Safety Evaluation of Oseltamivir (Tamiflu) in the Treatment of Infants 0 to < 12 months of Age with Confirmed Influenza Infection."

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:

N/A

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:

N/A

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"):

- Investigation #1 CASG 114 (WP20749): “A Pharmacokinetic/Pharmacodynamic and Safety Evaluation of Oseltamivir (Tamiflu) for the Treatment of Children Less Than 24 Months of Age with Confirmed Influenza Infection.”
- Investigation #2 WP22849: “An Open Label, Prospective, Pharmacokinetic/Pharmacodynamic, and Safety Evaluation of Oseltamivir (Tamiflu) in the Treatment of Infants 0 to < 12 months of Age with Confirmed Influenza Infection.”

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 # 71826 YES  NO   
 ! Explain:  
 NIH was sponsor of this IND



Name of Office/Division Director signing form: Debbie Birnkrant, M.D.  
Title: Division Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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

/s/  
-----

ELIZABETH G THOMPSON  
12/17/2012

DEBRA B BIRNKRANT  
12/17/2012

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

NDA: 21087 and 21246

Supplement Number: S-062  
and S-045

NDA Supplement Type (e.g. SE5): SE5  
(new patient population)

Division Name: DAVP

PDUFA Goal Date:  
December 21, 2012

Stamp Date: 6/21/2012

Proprietary Name: TAMIFLU

Established/Generic Name: oseltamivir phosphate

Dosage Form: Capsules- 30, 45, and 75 mg; Oral Suspension- 6 mg/mL

Applicant/Sponsor: Hoffmann-La Roche, Inc.

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

(1) treatment of uncomplicated acute illness due to influenza infection in patients 1 year and older who have been symptomatic for no more than 2 days

(2) prophylaxis of influenza in patients 1 year and older

(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): 0

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

**Indication:** same as above

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

Yes  Continue

No  Please proceed to Question 2.

If Yes, NDA/BLA#: \_\_\_\_\_

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

<b>Section A:</b> 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: \_\_\_\_\_

† 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*

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

*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 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}*

Regulatory Project Manager

(Revised: 6/2008)

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

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

/s/  
-----

ELIZABETH G THOMPSON  
12/14/2012

### 1.3.3 Debarment Certification for Study CASG114 (WP20749)



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health  
National Institute of Allergy  
and Infectious Diseases  
Bethesda, Maryland 20892

#### MEMORANDUM

**DATE:** August 9, 2011  
**FROM:** Office of Regulatory Affairs (ORA), DMID, NIAID, NIH  
**SUBJECT:** DMID Protocol No. 06-0056/CASG114 /WP-20749  
**Debarment Certification**  
**TO:** Cynthia Dillon, Associate Director, Regulatory Affairs, Hoffmann-La Roche

#### DEBARMENT CERTIFICATION

The sponsor of DMID Protocol No. 06-0059 (CASG114), the Division of Microbiology and Infectious Diseases (DMID) at the National Institute of Allergy and Infectious Diseases (NIAID), hereby certifies that it did not and will not knowingly use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with DMID Protocol No. 06-0059.

A handwritten signature in black ink that reads "Robert Johnson".

Robert Johnson, PhD  
Director, ORA, DMID, NIAID, NIH  
6610 Rockledge Drive, Room 4706  
Bethesda, MD 20892-6603  
Branch Phone: # 301-402-2126  
Fax: # 301-402-0804

Aug. 9<sup>th</sup> 2011  
Date

**Confidential Not for Unauthorized Distribution**

U.S. NDA: Tamiflu<sup>®</sup>—Hoffmann-La Roche, Inc.  
1/Regional (Influenza): 1-3-3.doc

**1.3.3 Debarment Certification for Study WP22849**

**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 # 21087 NDA # 21246	NDA Supplement # 062 NDA Supplement # 045	If NDA, Efficacy Supplement Type: New patient population (SE5); pediatric
Proprietary Name: TAMIFLU Established/Proper Name: oseltamivir phosphate Dosage Form: 30, 45, 75 mg capsules and 6 mg/mL powder for oral suspension		Applicant: Hoffmann-La Roche, Inc. Agent for Applicant (if applicable): Genentech
RPM: Elizabeth Thompson		Division: DAVP
<p><b><u>NDA and NDA Efficacy Supplements:</u></b></p> <p>NDA Application Type: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) 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 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)</p>		<p><b><u>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</u></b></p> <p>Listed drug(s) relied upon for approval (include NDA #(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"/> This application does not rely upon a listed drug.  <input type="checkbox"/> This application relies on literature.  <input type="checkbox"/> This application relies on a final OTC monograph.  <input type="checkbox"/> This application relies on (explain)</p> <p><b><u>For ALL (b)(2) applications, two months prior to EVERY action, review the information in the 505(b)(2) Assessment and submit the draft<sup>2</sup> to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</u></b></p> <p><b><u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u></b></p> <p><input type="checkbox"/> No changes    <input type="checkbox"/> Updated    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>
❖ Actions		
<ul style="list-style-type: none"> <li>• Proposed action</li> <li>• User Fee Goal Date is <u>December 21, 2012</u></li> </ul>		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <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 checked="" type="checkbox"/> None

<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.

<sup>2</sup> For resubmissions, (b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).



❖ 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 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 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 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 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 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 <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) <input type="checkbox"/> Verified 21 CFR 314.50(i)(1) <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 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) <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
---	--

**CONTENTS OF ACTION PACKAGE**

❖ Copy of this Action Package Checklist <sup>4</sup>	Included
<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) Approval: December 21, 2012
<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 draft labeling. If it is division-proposed labeling, it should be in track-changes format.</li> </ul>	December 21, 2012
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	June 21, 2012
<ul style="list-style-type: none"> <li>• Example of class labeling, if applicable</li> </ul>	N/A

<sup>4</sup> Fill in blanks with dates of reviews, letters, etc.

❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling ( <i>write submission/communication date at upper right of first page of each piece</i> )	<input type="checkbox"/> Medication Guide <input checked="" type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
<ul style="list-style-type: none"> <li>Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.</li> </ul>	December 21, 2012
<ul style="list-style-type: none"> <li>Original applicant-proposed labeling</li> </ul>	June 21, 2012
<ul style="list-style-type: none"> <li>Example of class labeling, if applicable</li> </ul>	N/A
❖ 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> )	
<ul style="list-style-type: none"> <li>Most-recent draft labeling</li> </ul>	N/A
❖ Proprietary Name <ul style="list-style-type: none"> <li>Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>)</li> <li>Review(s) (<i>indicate date(s)</i>)</li> <li>Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name.</li> </ul>	N/A N/A
❖ Labeling reviews ( <i>indicate dates of reviews and meetings</i> )	<input checked="" type="checkbox"/> RPM: 8-28-12; 12-21-12 <input checked="" type="checkbox"/> OSE/DMEPA: 11-16-12 <input checked="" type="checkbox"/> OMPI/DMPP: 12-10-12 <input checked="" type="checkbox"/> ODPD/DPDP: 12-7-12 <input checked="" type="checkbox"/> OPDP/DCDP: 12-12-12 <input type="checkbox"/> SEALD <input type="checkbox"/> CSS
<b>Administrative / Regulatory Documents</b>	
❖ Administrative Reviews ( <i>e.g., RPM Filing Review<sup>5</sup>/Memo of Filing Meeting</i> ) ( <i>indicate date of each review</i> )	August 20, 2012
❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte	<input checked="" type="checkbox"/> Not a (b)(2)
❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment ( <i>indicate date</i> )	<input checked="" type="checkbox"/> Not a (b)(2)
❖ NDAs only: Exclusivity Summary ( <i>signed by Division Director</i> )	<input checked="" type="checkbox"/> Included
❖ Application Integrity Policy (AIP) Status and Related Documents <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a>	
<ul style="list-style-type: none"> <li>Applicant is 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  <input type="checkbox"/> Not an AP action
❖ Pediatrics ( <i>approvals only</i> ) <ul style="list-style-type: none"> <li>Date reviewed by PeRC <u>N/A</u>            If PeRC review not necessary, explain: <u>supplements are new patient population therefore PREA not triggered</u></li> <li>Pediatric Page/Record (<i>approvals only, must be reviewed by PERC before finalized</i>)</li> </ul>	<input checked="" type="checkbox"/> Included

<sup>5</sup> Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

❖ 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>	<input checked="" type="checkbox"/> Verified, statement is acceptable
❖ Outgoing communications <i>(letters, including response to FDRR (do not include previous action letters in this tab), emails, faxes, telecons)</i>	Included
❖ Internal memoranda, telecons, etc.	Included
❖ Minutes of Meetings	
• Regulatory Briefing <i>(indicate date of mtg)</i>	<input checked="" type="checkbox"/> No mtg
• If not the first review cycle, any end-of-review meeting <i>(indicate date of mtg)</i>	<input checked="" type="checkbox"/> N/A or no mtg
• 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 milestone meetings (e.g., EOP2a, CMC pilots) <i>(indicate dates of mtgs)</i>	N/A
❖ Advisory Committee Meeting(s)	<input checked="" 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 December 13, 2012
PMR/PMC Development Templates <i>(indicate total number)</i>	<input checked="" type="checkbox"/> None
<b>Clinical Information<sup>6</sup></b>	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) <i>(indicate date for each review)</i>	See CDTL review
• Clinical review(s) <i>(indicate date for each review)</i>	November 28, 2012 (filing) December 10, 2012
• Social scientist review(s) (if OTC drug) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not <i>(indicate date of review/memo)</i>	See Clinical review (page 12)
❖ Clinical reviews from immunology and 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 applicable
❖ Risk Management	
• REMS Documents and Supporting Statement <i>(indicate date(s) of submission(s))</i>	N/A
• REMS Memo(s) and letter(s) <i>(indicate date(s))</i>	N/A
• Risk management 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>	<input checked="" type="checkbox"/> None N/A

<sup>6</sup> Filing reviews should be filed with the discipline reviews.

❖ DSI Clinical Inspection Review Summary(ies) (include copies of DSI letters to investigators)	<input checked="" type="checkbox"/> None requested
<b>Clinical Microbiology</b> <input type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
Clinical Microbiology Review(s) (indicate date for each review)	<input type="checkbox"/> None August 6, 2012 (filing) November 20, 2012
<b>Biostatistics</b> <input checked="" type="checkbox"/> None	
❖ Statistical Division Director Review(s) (indicate date for each review)	<input type="checkbox"/> None
Statistical Team Leader Review(s) (indicate date for each review)	<input type="checkbox"/> None
Statistical Review(s) (indicate date for each review)	<input type="checkbox"/> None
<b>Clinical Pharmacology</b> <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
Clinical Pharmacology Team Leader Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
Clinical Pharmacology review(s) (indicate date for each review)	<input type="checkbox"/> None August 3, 2012 (filing) November 27 and 30, 2012
❖ DSI Clinical Pharmacology Inspection Review Summary (include copies of DSI letters)	<input type="checkbox"/> None November 27, 2012 and November 28, 2012
<b>Nonclinical</b> <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
• Supervisory Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
• Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	<input type="checkbox"/> None November 30, 2012 (filing) December 3, 2012
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (indicate date for each review)	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None
❖ DSI Nonclinical Inspection Review Summary (include copies of DSI letters)	<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) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i>	<input type="checkbox"/> None Product Quality Review: August 6, 2012 ONDQA Biopharm Review: N/A
❖ Microbiology Reviews <input type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i> <input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) <i>(indicate date of each review)</i>	<input checked="" type="checkbox"/> Not needed
❖ 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 6, 2012
<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	
<input checked="" type="checkbox"/> NDAs: Facilities inspections (include EER printout) <i>(date completed must be within 2 years of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites<sup>7</sup>)</i>	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input checked="" type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER <i>(date of most recent TB-EER must be within 30 days of action date) (original and supplemental BLAs)</i>	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation <i>(check box only, do not include documents)</i>	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input checked="" type="checkbox"/> Not needed (per review)

<sup>7</sup> I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

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

/s/  
-----

ELIZABETH G THOMPSON  
12/21/2012

**From:** [Thompson, Elizabeth](#)  
**To:** [Maria Adriano](#)  
**Cc:** [Thompson, Elizabeth](#)  
**Subject:** Tamiflu: (b) (4)  
**Date:** Thursday, December 20, 2012 6:38:23 AM  
**Attachments:** [Tamiflu](#) (b) (4) [\\_Fox 12-18-2012.doc](#)  
**Importance:** High

---

Maria

Here is the Division's recommendations/revisions for the (b) (4)

Regards,

*Beth*

Elizabeth Thompson, M.S.  
LCDR, U.S. Public Health Service  
Regulatory Project Manager  
FDA/CDER/OND/DAVP  
10903 New Hampshire Avenue  
Bldg #22, Rm 6324  
Silver Spring, MD 20993  
301-796-0824 (office); 301-796-9883 (fax)  
elizabeth.thompson@fda.hhs.gov

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

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

/s/  
-----

ELIZABETH G THOMPSON  
12/20/2012

**From:** [Thompson, Elizabeth](#)  
**To:** [Maria Adriano](#)  
**Cc:** [Thompson, Elizabeth](#)  
**Subject:** Tamiflu: labeling  
**Date:** Thursday, December 20, 2012 10:15:03 AM  
**Attachments:** [PPI edit 12-20-12.doc](#)  
**Importance:** High

---

Maria-

The Division noted one last minor revision in the PPI (see attached).

We can handle this several ways:

1. If Roche has not submitted final labeling, and agrees, please revise and submit.
2. If Roche has submitted the final label electronically already, the Division can include the revision in our action letter (if you agree to the change), and labeling can be submitted after action as requested in the letter.

Please let me know which method works best for Roche.

Regards (and I do apologize for the last minute change)!

*Beth*

Elizabeth Thompson, M.S.  
LCDR, U.S. Public Health Service  
Regulatory Project Manager  
FDA/CDER/OND/DAVP  
10903 New Hampshire Avenue  
Bldg #22, Rm 6324  
Silver Spring, MD 20993  
301-796-0824 (office); 301-796-9883 (fax)  
elizabeth.thompson@fda.hhs.gov

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

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

/s/  
-----

ELIZABETH G THOMPSON  
12/20/2012

**From:** [Thompson, Elizabeth](#)  
**To:** [Maria Adriano](#)  
**Cc:** [Thompson, Elizabeth](#)  
**Subject:** RE: Tamiflu labeling  
**Date:** Wednesday, December 19, 2012 3:53:36 PM  
**Attachments:** [PPI comments 12-19-12.doc](#)  
[PI comments 12-19-12.doc](#)  
**Importance:** High

---

Maria-

Here are our comments for the PPI/IFU:

I have one additional edit to the PI (section 12.3):

Please let me know asap whether Roche agrees with the revisions to the PI and PPI/IFU so that I can finalize labeling and prepare for an action. Please submit clean and annotated versions of labeling to the pending supplements. Please confirm that the Division will receive these on/before December 21, 2012.

Regards,

*Beth*

Elizabeth Thompson, M.S.  
LCDR, U.S. Public Health Service  
Regulatory Project Manager  
FDA/CDER/OND/DAVP  
10903 New Hampshire Avenue  
Bldg #22, Rm 6324  
Silver Spring, MD 20993  
301-796-0824 (office); 301-796-9883 (fax)  
[elizabeth.thompson@fda.hhs.gov](mailto:elizabeth.thompson@fda.hhs.gov)

---

**From:** Thompson, Elizabeth  
**Sent:** Wednesday, December 19, 2012 12:05 PM  
**To:** Maria Adriano  
**Cc:** Thompson, Elizabeth  
**Subject:** Tamiflu labeling  
**Importance:** High

Maria-

The Division agrees with your proposed PI with the following minor edits (see attached):

<< File: clean PI 12-19-12.doc >>

If you agree, please submit officially to the pending peds supplements (S-060 and S-045). I should have the PPI review done soon and will let you know if we agree or have any other minor edits.

We will take action upon receipt. If these cannot be submitted electronically in time, please prepare the submission and provide me with an email copy so I can verify the date of the cover letter and 356h.

Regards,

*Beth*

Elizabeth Thompson, M.S.  
LCDR, U.S. Public Health Service  
Regulatory Project Manager  
FDA/CDER/OND/DAVP  
10903 New Hampshire Avenue  
Bldg #22, Rm 6324  
Silver Spring, MD 20993  
301-796-0824 (office); 301-796-9883 (fax)  
elizabeth.thompson@fda.hhs.gov

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

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

/s/  
-----

ELIZABETH G THOMPSON  
12/20/2012

**From:** [Thompson, Elizabeth](#)  
**To:** [Maria Adriano](#)  
**Cc:** [Thompson, Elizabeth](#)  
**Subject:** Tamiflu peds: additional PI revisions  
**Date:** Friday, December 14, 2012 1:42:04 PM  
**Importance:** High

---

Maria-

As I continue to look at the label several times a day, I find more edits...I do apologize. I was trying to determine the best way to discuss with you, as the PDUFA clock is approaching and I have already sent our PI revisions annotated word version. I didn't want to send another word version, so thought I would just list them here.

- Section 2.3: Please edit title of first heading to Adults and Adolescents (13 years of age and older) to be consistent with heading in Section 2.2
- Section 6.1: Please consider changing the heading to be consistent with other sections. For example, Treatment Studies in Adult and Adolescent Subjects (13 years of age and older) and Prophylaxis Studies in Adult and Adolescent Subjects (13 years of age and older)
- Table 7: change "Patients" to "Subjects" in title
- Section 14.1: Please consider changing the heading to be consistent with other sections. For example, Adult and Adolescents (13 years of age and older)
- Section 14.2: Please consider changing the heading to be consistent with other sections. For example, Adult and Adolescents (13 years of age and older)
- Section 17: Since an Instructions for Use has been added, please revise to read "See FDA-approved Patient Labeling (Patient Information and Instructions for Use)

If you need to discuss, please feel free to call or email.

Regards,

*Beth*

Elizabeth Thompson, M.S.  
LCDR, U.S. Public Health Service  
Regulatory Project Manager  
FDA/CDER/OND/DAVP  
10903 New Hampshire Avenue  
Bldg #22, Rm 6324  
Silver Spring, MD 20993  
301-796-0824 (office); 301-796-9883 (fax)  
[elizabeth.thompson@fda.hhs.gov](mailto:elizabeth.thompson@fda.hhs.gov)

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

/s/  
-----

ELIZABETH G THOMPSON  
12/14/2012

**From:** [Thompson, Elizabeth](#)  
**To:** [Thompson, Elizabeth](#)  
**Subject:** FW: Tamiflu peds supplements: Division proposed labeling  
**Date:** Friday, December 14, 2012 2:55:18 PM  
**Importance:** High

---

**From:** Thompson, Elizabeth  
**Sent:** Tuesday, December 11, 2012 8:04 AM  
**To:** 'Maria Adriano'  
**Cc:** Thompson, Elizabeth  
**Subject:** RE: Tamiflu peds supplements: Division proposed labeling  
**Importance:** High

[Maria-](#)

We are working on a response to your proposed label changes to the PI and will also have major revisions to the PPI. For now, the Division has the following comment for clarification:

Your integrated database (sdemog file) contains records for 126 subjects, with notation that #45 has no treatment begin date. However, from the Clinical Summary, it appeared that 2 of these subjects were never dosed and had no post-baseline information. Please clarify whether Subject #234 received any doses of Tamiflu. The description of the clinical trial population can be modified to appropriately describe the population (e.g., 135/136 subjects who were enrolled and received Tamiflu, or 135 subjects with available safety data).

*Beth*

Elizabeth Thompson, M.S.  
LCDR, U.S. Public Health Service  
Regulatory Project Manager  
FDA/CDER/OND/DAVP  
10903 New Hampshire Avenue  
Bldg #22, Rm 6324  
Silver Spring, MD 20993  
301-796-0824 (office); 301-796-9883 (fax)  
elizabeth.thompson@fda.hhs.gov

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

/s/  
-----

ELIZABETH G THOMPSON  
12/14/2012

**From:** Thompson, Elizabeth  
**To:** ["Maria Adriano"](#)  
**Subject:** RE: Tamiflu peds supplements: Division proposed labeling (PPI)  
**Date:** Thursday, December 13, 2012 4:15:00 PM  
**Attachments:** [Division PPI comments.doc](#)  
**Importance:** High

---

Maria-

We revised slightly. This version differs from the last in that we added information about receiving influenza vaccine (OPDP comment) and we removed (b) (4)

I apologize for the multiple emails and revisions.

Regards,

*Beth*

Elizabeth Thompson, M.S.  
LCDR, U.S. Public Health Service  
Regulatory Project Manager  
FDA/CDER/OND/DAVP  
10903 New Hampshire Avenue  
Bldg #22, Rm 6324  
Silver Spring, MD 20993  
301-796-0824 (office); 301-796-9883 (fax)  
elizabeth.thompson@fda.hhs.gov

---

**From:** Maria Adriano [mailto:[adriano.maria@gene.com](mailto:adriano.maria@gene.com)]  
**Sent:** Thursday, December 13, 2012 3:30 PM  
**To:** Thompson, Elizabeth  
**Cc:** Maria Adriano  
**Subject:** Re: Tamiflu peds supplements: Division proposed labeling (PPI)

Dear Beth,

I confirm receipt of these comments and will submit both the PI and PPI together.

Best regards,  
Maria Adriano, MS, MBA, RAC

Product Development Regulatory  
W: 650.467.7339  
M: 650.296.2585

On Thu, Dec 13, 2012 at 12:22 PM, Thompson, Elizabeth  
<[Elizabeth.Thompson@fda.hhs.gov](mailto:Elizabeth.Thompson@fda.hhs.gov)> wrote:

Maria-

The Division is forwarding comments from DDMAC (OPDP) and Patient Labeling (DMPP) for the PPI. Again, the PPI for Tamiflu underwent some extensive revisions. The Division would like a response to our proposed labeling by Tuesday, December 18, 2012. You can hold off on submitting electronically until both parties agree on PI and PPI.

Regards,

*Beth*

Elizabeth Thompson, M.S.  
LCDR, U.S. Public Health Service  
Regulatory Project Manager  
FDA/CDER/OND/DAVP  
10903 New Hampshire Avenue  
Bldg #22, Rm 6324  
Silver Spring, MD 20993  
[301-796-0824](tel:301-796-0824) (office); [301-796-9883](tel:301-796-9883) (fax)  
[elizabeth.thompson@fda.hhs.gov](mailto:elizabeth.thompson@fda.hhs.gov)

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

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

/s/  
-----

ELIZABETH G THOMPSON  
12/14/2012

**From:** [Thompson, Elizabeth](#)  
**To:** [Thompson, Elizabeth](#)  
**Subject:** FW: Tamiflu peds supplements: Division proposed labeling  
**Date:** Friday, December 14, 2012 2:55:18 PM  
**Importance:** High

---

**From:** Thompson, Elizabeth  
**Sent:** Tuesday, December 11, 2012 8:04 AM  
**To:** 'Maria Adriano'  
**Cc:** Thompson, Elizabeth  
**Subject:** RE: Tamiflu peds supplements: Division proposed labeling  
**Importance:** High

[Maria-](#)

We are working on a response to your proposed label changes to the PI and will also have major revisions to the PPI. For now, the Division has the following comment for clarification:

Your integrated database (sdemog file) contains records for 126 subjects, with notation that #45 has no treatment begin date. However, from the Clinical Summary, it appeared that 2 of these subjects were never dosed and had no post-baseline information. Please clarify whether Subject #234 received any doses of Tamiflu. The description of the clinical trial population can be modified to appropriately describe the population (e.g., 135/136 subjects who were enrolled and received Tamiflu, or 135 subjects with available safety data).

*Beth*

Elizabeth Thompson, M.S.  
LCDR, U.S. Public Health Service  
Regulatory Project Manager  
FDA/CDER/OND/DAVP  
10903 New Hampshire Avenue  
Bldg #22, Rm 6324  
Silver Spring, MD 20993  
301-796-0824 (office); 301-796-9883 (fax)  
elizabeth.thompson@fda.hhs.gov

**From:** Thompson, Elizabeth  
**To:** ["Maria Adriano"](#)  
**Cc:** [Thompson, Elizabeth](#)  
**Subject:** Tamiflu peds supplements: Division proposed labeling (PI)  
**Date:** Wednesday, December 12, 2012 3:48:00 PM  
**Attachments:** [Division PI comments 2.doc](#)  
**Importance:** High

---

Maria-

Please confirm receipt of this email.

The Division has more comments on the PI (after consultation with our labeling groups here at FDA). Please review our proposed changes and provide a response by Monday December 17, 2012. Please let me know if you have any questions. The Division's proposed changes to the PPI should be coming either later today or tomorrow.

Again, you can provide this version by email. Once we have agreement on both the PI and PPI, I will have you submit officially.

Regards,

*Beth*

Elizabeth Thompson, M.S.  
LCDR, U.S. Public Health Service  
Regulatory Project Manager  
FDA/CDER/OND/DAVP  
10903 New Hampshire Avenue  
Bldg #22, Rm 6324  
Silver Spring, MD 20993  
301-796-0824 (office); 301-796-9883 (fax)  
elizabeth.thompson@fda.hhs.gov

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

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

/s/  
-----

ELIZABETH G THOMPSON  
12/14/2012



NDA 21087/S-062  
NDA 21246/S-045

**LABELING PMR/PMC DISCUSSION COMMENTS**

Hoffmann-La Roche, Inc.  
Attention: Maria Adriano  
c/o Genentech, Inc.  
1 DNA Way, MS#241B  
South San Francisco, CA 94080-4990

Dear Ms. Adriano:

Please refer to your June 21, 2012 Supplemental New Drug Applications (sNDAs) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for TAMIFLU (oseltamivir phosphate) 30, 45 and 75 mg capsules and TAMIFLU (oseltamivir phosphate) 6 mg/mL powder for oral suspension.

We also refer to our July 2, 2012, letter in which we notified you of our target date of November 30, 2012 for communicating labeling changes and/or postmarketing requirements/commitments in accordance with the "PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES – FISCAL YEARS 2008 THROUGH 2012."

We received your August 29, 2012 proposed labeling submission to this application, and have proposed revisions which are included as an enclosure. These revisions have been reviewed and cleared to the level of Cross Discipline Team Leader.

If you have any questions, please contact Elizabeth Thompson, M.S., Regulatory Project Manager, at (301) 796-0824 or via email at [elizabeth.thompson@fda.hhs.gov](mailto:elizabeth.thompson@fda.hhs.gov).

Sincerely,

*{See appended electronic signature page}*

Elizabeth Thompson, M.S.  
LCDR, U.S. Public Health Service  
Regulatory Project Manager  
Division of Antiviral Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research

ENCLOSURE: Division proposed labeling

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

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

/s/  
-----

ELIZABETH G THOMPSON  
11/30/2012



## ELECTRONIC MAIL CORRESPONDENCE- INFORMATION REQUEST

**Date:** November 2, 2012

**To:** Maria Adriano  
Regulatory Program Director, Regulatory Affairs  
Hoffmann-La Roche, Inc. c/o Genentech, Inc.

**From:** Elizabeth Thompson, M.S.  
Regulatory Project Manager  
Division of Antiviral Products

**NDA/Drug:** 21087/TAMIFLU (oseltamivir phosphate) Capsules  
21246/TAMIFLU (oseltamivir phosphate) for Oral Suspension

**Subject:** Communication Plans: Division comments

Please refer to your [REDACTED] (b) (4)

[REDACTED] We also refer to your general correspondence submission dated October 5, 2012, which provided your draft communication plan and Dear Pharmacist Letter. We have the following comments:

### Communication Plans

In general we agree with the timing and details of your communication plans for the above supplements. [REDACTED] (b) (4)

### Dear Pharmacist Letter

We have the following initial comments for your review, but will provide any additional comments once labeling discussions have been finalized for the pending ped efficacy supplement.

Consider revising the sentences after the paragraph that begins [REDACTED] (b) (4) to the following to bring more prominence to the important dispensing information:

### Dispensing Information:

1. Small volumes will be involved when dispensing for patients less than 1 year of age.
2. Remove 10 mL dosing device from packaging when dispensing to patients less than 1 year of age.
3. Provide the appropriate dosing device that can accurately measure and administer these smaller volumes.

PLEASE REPLY BY EMAIL ([Elizabeth.thompson@fda.hhs.gov](mailto:Elizabeth.thompson@fda.hhs.gov)) to confirm receipt. If you have any questions regarding the contents of this correspondence, please contact me by email or phone (301-796 0824).

*{See appended electronic signature page}*

---

Elizabeth Thompson, M.S.  
LCDR, U.S. Public Health Service  
Regulatory Project Manager  
Division of Antiviral Products  
Center for Drug Evaluation and Research  
Food and Drug Administration

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

/s/  
-----

ELIZABETH G THOMPSON  
11/02/2012



## ELECTRONIC MAIL CORRESPONDENCE- INFORMATION REQUEST

**Date:** September 11, 2012

**To:** Sarah Oliver, Ph.D.  
Associate Program Director, Regulatory Affairs  
Hoffmann-La Roche, Inc. c/o Genentech, Inc.

**From:** Elizabeth Thompson, M.S.  
Regulatory Project Manager  
Division of Antiviral Products

**NDA/Drug:** 21087/TAMIFLU (oseltamivir phosphate) Capsules  
21246/TAMIFLU (oseltamivir phosphate) for Oral Suspension

**Subject:** Pending Efficacy Supplement: Clinical Comments

---

Please refer to your pending Efficacy Supplements dated June 21, 2012 (NDA 21087/S-062 and NDA 21246/S-045). We have the following request for information.

### Clinical

1. We are unable to corroborate the numbers of adverse events (AEs) you have provided in your submission. According to the CASG 114 study report, there were 99 on-treatment non-serious AEs (excluding serious AEs) in 53 subjects. In the WP22849 study report, you identify a total of 48 on-treatment AEs in 32 subjects. Instead of a total 147 AEs in 85 subjects, you state in your Study Overview that when pooled from both studies, you found a total of 89 AEs in 61 subjects. Please explain this discrepancy.

PLEASE REPLY BY EMAIL ([Elizabeth.thompson@fda.hhs.gov](mailto:Elizabeth.thompson@fda.hhs.gov)) to confirm receipt. If you have any questions regarding the contents of this correspondence, please contact me by email or phone (301-796 0824).

*{See appended electronic signature page}*

---

Elizabeth Thompson, M.S.  
LCDR, U.S. Public Health Service  
Regulatory Project Manager  
Division of Antiviral Products  
Center for Drug Evaluation and Research  
Food and Drug Administration

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

/s/  
-----

ELIZABETH G THOMPSON  
09/11/2012



## ELECTRONIC MAIL CORRESPONDENCE- INFORMATION REQUEST

**Date:** August 31, 2012

**To:** Sarah Oliver, Ph.D.  
Associate Program Director, Regulatory Affairs  
Hoffmann-La Roche, Inc. c/o Genentech, Inc.

**From:** Elizabeth Thompson, M.S.  
Regulatory Project Manager  
Division of Antiviral Products

**NDA/Drug:** 21087/TAMIFLU (oseltamivir phosphate) Capsules  
21246/TAMIFLU (oseltamivir phosphate) for Oral Suspension

**Subject:** Pending Efficacy Supplement: Request for Information

---

Please refer to your pending Efficacy Supplements dated June 21, 2012 (NDA 21087/S-062 and NDA 21246/S-045). We have the following request for information.

### Clinical Virology

The resistance datasets for WP20749 (CASG114) appear to be missing the data for Cohorts I-A and I-B. Please submit the data or reference the file name and directory location of the data.

PLEASE REPLY BY EMAIL ([Elizabeth.thompson@fda.hhs.gov](mailto:Elizabeth.thompson@fda.hhs.gov)) to confirm receipt. If you have any questions regarding the contents of this correspondence, please contact me by email or phone (301-796 0824).

*{See appended electronic signature page}*

---

Elizabeth Thompson, M.S.  
LCDR, U.S. Public Health Service  
Regulatory Project Manager  
Division of Antiviral Products  
Center for Drug Evaluation and Research  
Food and Drug Administration

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

/s/  
-----

ELIZABETH G THOMPSON  
08/31/2012



## ELECTRONIC MAIL CORRESPONDENCE- INFORMATION REQUEST

**Date:** August 29, 2012

**To:** Sarah Oliver, Ph.D.  
Associate Program Director, Regulatory Affairs  
Hoffmann-La Roche, Inc. c/o Genentech, Inc.

**From:** Elizabeth Thompson, M.S.  
Regulatory Project Manager  
Division of Antiviral Products

**NDA/Drug:** 21087/TAMIFLU (oseltamivir phosphate) Capsules  
21246/TAMIFLU (oseltamivir phosphate) for Oral Suspension

**Subject:** Pending Efficacy Supplement: Request for Information

---

Please refer to your pending Efficacy Supplements dated June 21, 2012 (NDA 21087/S-062 and NDA 21246/S-045). We have the following request for information.

### Clinical Virology

The Division would like to update the TAMIFLU label to include recently identified substitutions associated with oseltamivir resistance. Please provide an updated list of substitutions that have been associated with clinical resistance (regardless of susceptibility) or reduced susceptibility to oseltamivir, including hemagglutinin substitutions identified in cell culture selection studies. Please include references.

PLEASE REPLY BY EMAIL ([Elizabeth.thompson@fda.hhs.gov](mailto:Elizabeth.thompson@fda.hhs.gov)) to confirm receipt. If you have any questions regarding the contents of this correspondence, please contact me by email or phone (301-796 0824).

*{See appended electronic signature page}*

---

Elizabeth Thompson, M.S.  
LCDR, U.S. Public Health Service  
Regulatory Project Manager  
Division of Antiviral Products  
Center for Drug Evaluation and Research  
Food and Drug Administration

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

/s/  
-----

ELIZABETH G THOMPSON  
08/29/2012



NDA 21087/S-062  
NDA 21246/S-045

## FILING COMMUNICATION

Hoffmann-La Roche, Inc.  
Attention: Sarah Oliver, Ph.D.  
Associate Program Director, Regulatory Affairs  
340 Kingsland Street  
Nutley, NJ 07110-1199

Dear Dr. Oliver:

Please refer to your Supplemental New Drug Applications (sNDAs) dated June 21, 2012, received June 21, 2012 (NDA 21246) and June 22, 2012 (NDA 21087), submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for TAMIFLU (oseltamivir phosphate) 30, 45, and 75 mg capsules and TAMIFLU (oseltamivir phosphate) 6 mg/mL powder for oral suspension.

These supplemental applications propose to expand the patient population for the treatment of influenza in infants with a post conceptual age of <sup>(b)</sup><sub>(4)</sub> weeks to one year of age.

We have completed our filing review and have determined that your supplemental applications are sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), these supplemental applications are considered filed 60 days after the date we received your supplemental applications. The review classification for these supplemental applications is **Priority**. Therefore, the user fee goal date is December 21, 2012.

We are reviewing your supplemental applications according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by November 30, 2012.

At this time we are notifying you that we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the supplemental application and is not indicative of deficiencies that may be identified during our review.

We have the following comments and requests for information:

### Clinical

1. In your proposed draft labeling, you are seeking to expand the indication for treatment of influenza with Tamiflu down to (b)(4) weeks of post-conceptual age. Please provide a summary of available data in infants less than (b)(4) weeks post-conceptual age and justification for the age limits for your proposed indication.
2. Please indicate where in the submission the coding dictionary is located, or submit the dictionary for our review. Alternatively, please explain your procedures for converting verbatim terms to MedDRA terms.

### Clinical Pharmacology (Pharmacometrics)

3. Provide all data included in your population PK database used for Simulation (Report titled "Population PK Analysis of Oseltamivir in Infants Less Than One-Year Old", dated March 13, 2012)
  - *Adult patients administered 75 mg BID doses: 93 subjects from Study WP16263*
  - *Adult patients administered 150 mg BID doses: 20 subjects from Study WV15670*
  - *Adult patients administered 225 mg BID doses: 94 subjects from Study WP16263*
  - *Adult patients administered 450 mg BID doses: 99 subjects from Study WP16263*
  - *1-2 year old patients administered 30 mg single doses: 12 subjects from Study PP16351*
  - *3-5 year old patients administered 45 mg single doses : 12 subjects from Study PP16351*
4. Provide all other available PK/PD data including children 1-2 years of age. These should include data from Studies JV16284 and WV15758 where significant number of patients developed resistance following 2 mg/kg dose.

Please respond only to the above requests for 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.

### **PROMOTIONAL MATERIAL**

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI) and patient PI (PPI). Submit

consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotion (OPDP)  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

Do not submit launch materials until you have received our proposed revisions to the package insert (PI) and patient PI (PPI), and you believe the labeling is close to the final version. For more information regarding OPDP submissions, please see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>. If you have any questions, call OPDP at 301-796-1200.

### **REQUIRED PEDIATRIC ASSESSMENTS**

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria apply to your application, you are exempt from this requirement.

If you have any questions, call Elizabeth Thompson, M.S., Regulatory Project Manager, at (301) 796-0824.

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

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

/s/  
-----

DEBRA B BIRNKRANT  
08/20/2012



NDA 21087/S-062  
NDA 21246/S-045

## INFORMATION REQUEST

Hoffmann-La Roche, Inc.  
Attention: Sarah Oliver, Ph.D.  
Associate Program Director, Regulatory Affairs  
340 Kingsland Street  
Nutley, NJ 07110-1199

Dear Dr. Oliver:

Please refer to your supplemental new drug applications submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for TAMIFLU (oseltamivir phosphate) 30, 45, 75 mg capsules and TAMIFLU (oseltamivir phosphate) 6 mg/mL powder for oral suspension.

We also refer to your submission dated June 21, 2012.

We are reviewing the Clinical and Clinical Pharmacology sections of your submission and have the following comments and information requests. We request a prompt written response within one week in order to continue our evaluation of your supplemental applications.

PLEASE PROVIDE THE FOLLOWING INFORMATION ON OR BEFORE AUGUST 8, 2012

### Clinical

1. We note that you have decided not to include in the pooled analysis data from the 11 subjects who developed influenza during the 2011/2012 season. Given the small number of pediatric subjects studied in total, complete information is imperative. Please submit the datasets for these 11 subjects, and we will incorporate the data into our own analyses. Please also submit any evaluation and conclusions you have made from these data, including information on demographics, PK parameters, and any additional information that you have collected.

### Clinical Pharmacology

2. In anticipation of a need for site inspections, please provide the full bioanalytical report(s) for plasma samples analyzed in trial CASG114 along with complete site information.
3. Please provide the number of subjects under 1 year of age at each clinical site for trial CASG114 along with complete site information.

If you have questions, call Elizabeth Thompson, M.S., Regulatory Project Manager, at (301) 796-0824.

Sincerely,

*{See appended electronic signature page}*

Elizabeth Thompson, M.S.  
LCDR, U.S. Public Health Service  
Regulatory 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.**  
-----

/s/  
-----

ELIZABETH G THOMPSON  
08/01/2012

MEMORANDUM

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

DATE: July 17, 2012

**SUBJECT: TAMIFLU Pediatric Supplements**

**APPLICATIONS: NDA 21087/S-062  
NDA 21246/S-045**

On June 21, 2012, the Division of Antiviral Products (DAVP) received efficacy supplements for Tamiflu. These supplements expanded the treatment patient population to less than one year of age. Labeling included revisions to the Indications and Usage, Dosage and Administration, Warnings and Precautions, Adverse Reactions, Use in Specific Populations, Clinical Pharmacology and Clinical Studies sections of the Prescribing Information.

The Division classified these efficacy supplements as “new patient population” and therefore PREA was not triggered. However, since these supplements were also pediatric, the Division contacted the Pediatrics staff to verify if PeRC would be required for the supplements. After discussing with Rosemary Addy/George Greeley, it was agreed upon that these supplements were not in response to PREA/BPCA (studies under one were waived) and do not trigger PREA. For coding purposes and for tracking in DARRTS, it was recommended to also classify these supplements as pediatric.

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

/s/  
-----

ELIZABETH G THOMPSON  
07/17/2012



NDA 21087/S-062  
NDA 21246/S-045

**ACKNOWLEDGEMENT --  
PRIOR APPROVAL SUPPLEMENT**

Hoffmann-La Roche, Inc.  
Attention: Sarah Oliver, Ph.D.  
Associate Program Director, Regulatory Affairs  
340 Kingsland Street  
Nutley, NJ 07110-1199

Dear Dr. Oliver:

We have received your Supplemental New Drug Applications (sNDAs) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA or the Act) for the following:

**NDA NUMBER:** 21087 and 21246

**SUPPLEMENT NUMBER:** 062 and 045

**PRODUCT NAME:** TAMIFLU (oseltamivir phosphate) capsules (30, 45, and 75 mg) and (6 mg/mL) powder for oral suspension

**DATE OF SUBMISSION:** June 21, 2012

**DATE OF RECEIPT:** June 21, 2012

These supplemental applications provides for a new dosage regimen for the treatment of influenza in infants under the age of 1 (post conceptional age of (b)(4) weeks to one year).

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 AUGUST 20, 2012, 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/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. 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 conform to the content and format requirements of revised 21 CFR 201.56-57.

**FDAAA TITLE VIII RESPONSIBILITIES**

You are also responsible for complying with the applicable provisions of sections 402(i) and (j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by

Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

### **SUBMISSION REQUIREMENTS**

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

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, see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

If you have any questions, please contact Elizabeth Thompson, M.S., Regulatory Project Manager, at (301) 796-0824 or via email at [elizabeth.thompson@fda.hhs.gov](mailto:elizabeth.thompson@fda.hhs.gov).

Sincerely,

*{See appended electronic signature page}*

Elizabeth Thompson, M.S.  
LCDR, U.S. Public Health Service  
Regulatory 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.**  
-----

/s/  
-----

ELIZABETH G THOMPSON  
07/02/2012