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?
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
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 ☐
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 [x]

   Investigation #2
   
   YES [ ]  NO [x]

   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?
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 ☒

NIH was sponsor of this 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

YES ☐ NO ☒

Explain: Roche only provided study drug to NIH

Investigation #2

YES ☒ NO ☐

Explain: Conducted in EU; protocol provided to IND 53093

(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:

N/A

=================================================================

Name of person completing form:  Elizabeth Thompson, M.S.
Title:  Regulatory Project Manager
Date:  December 17, 2012
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 and SE6 (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.)

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).*

<table>
<thead>
<tr>
<th>Reason (see below for further detail):</th>
<th>minimum</th>
<th>maximum</th>
<th>Not feasible</th>
<th>Not meaningful therapeutic benefit</th>
<th>Ineffective or unsafe†</th>
<th>Formulation failed∆</th>
</tr>
</thead>
<tbody>
<tr>
<td>☐ Neonate</td>
<td>__ wk. __ mo.</td>
<td>__ wk. __ mo.</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>☐ Other</td>
<td>__ yr. __ mo.</td>
<td>__ yr. __ mo.</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>☐ Other</td>
<td>__ yr. __ mo.</td>
<td>__ yr. __ mo.</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>☐ Other</td>
<td>__ yr. __ mo.</td>
<td>__ yr. __ mo.</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
</tbody>
</table>

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.)

- ∆ 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

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

Reference ID: 3230941
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):

<table>
<thead>
<tr>
<th>Deferrals (for each or all age groups):</th>
<th>Reason for Deferral</th>
<th>Applicant Certification †</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td>Ready for Approval in Adults</td>
<td>Need Additional Adult Safety or Efficacy Data</td>
</tr>
<tr>
<td>Neonate</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>wk. __ wk. __</td>
<td></td>
</tr>
<tr>
<td></td>
<td>mo. mo.</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>yr. __ yr. __</td>
<td></td>
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<tr>
<td></td>
<td>mo. mo.</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>yr. __ yr. __</td>
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</tr>
<tr>
<td></td>
<td>mo. mo.</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>yr. __ yr. __</td>
<td></td>
</tr>
<tr>
<td></td>
<td>mo. mo.</td>
<td></td>
</tr>
<tr>
<td>All Pediatric Populations</td>
<td>Ready for Approval in Adults</td>
<td>Need Additional Adult Safety or Efficacy Data</td>
</tr>
<tr>
<td></td>
<td>wk. __ wk. __</td>
<td></td>
</tr>
<tr>
<td></td>
<td>mo. mo.</td>
<td></td>
</tr>
<tr>
<td>Date studies are due (mm/dd/yy):</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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):**

<table>
<thead>
<tr>
<th>Population</th>
<th>minimum</th>
<th>maximum</th>
<th>PeRC Pediatric Assessment form attached?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonate</td>
<td>__ wk. __ mo.</td>
<td>__ wk. __ mo.</td>
<td>Yes ☐ No ☐</td>
</tr>
<tr>
<td>Other</td>
<td>__ yr. __ mo.</td>
<td>__ yr. __ mo.</td>
<td>Yes ☐ No ☐</td>
</tr>
<tr>
<td>Other</td>
<td>__ yr. __ mo.</td>
<td>__ yr. __ mo.</td>
<td>Yes ☐ No ☐</td>
</tr>
<tr>
<td>Other</td>
<td>__ yr. __ mo.</td>
<td>__ yr. __ mo.</td>
<td>Yes ☐ No ☐</td>
</tr>
<tr>
<td>All Pediatric Subpopulations</td>
<td>0 yr. 0 mo.</td>
<td>16 yr. 11 mo.</td>
<td>Yes ☐ No ☐</td>
</tr>
</tbody>
</table>

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:**

<table>
<thead>
<tr>
<th>Population</th>
<th>minimum</th>
<th>maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonate</td>
<td>__ wk. __ mo.</td>
<td>__ wk. __ mo.</td>
</tr>
<tr>
<td>Other</td>
<td>__ yr. __ mo.</td>
<td>__ yr. __ mo.</td>
</tr>
<tr>
<td>Other</td>
<td>__ yr. __ mo.</td>
<td>__ yr. __ mo.</td>
</tr>
<tr>
<td>Other</td>
<td>__ yr. __ mo.</td>
<td>__ yr. __ mo.</td>
</tr>
<tr>
<td>All Pediatric Subpopulations</td>
<td>0 yr. 0 mo.</td>
<td>16 yr. 11 mo.</td>
</tr>
</tbody>
</table>

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

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Reference ID: 3230941
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:

<table>
<thead>
<tr>
<th>Population</th>
<th>minimum</th>
<th>maximum</th>
<th>Extrapolated from:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Adult Studies?</td>
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<td></td>
<td>Other Pediatric</td>
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<td></td>
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<td></td>
<td>Studies?</td>
</tr>
<tr>
<td>Neonate</td>
<td>__ wk. __ mo.</td>
<td>__ wk. __ mo.</td>
<td>☐</td>
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<tr>
<td>Other</td>
<td>__ yr. __ mo.</td>
<td>__ yr. __ mo.</td>
<td>☐</td>
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<tr>
<td>Other</td>
<td>__ yr. __ mo.</td>
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<tr>
<td>Other</td>
<td>__ yr. __ mo.</td>
<td>__ yr. __ mo.</td>
<td>☐</td>
</tr>
<tr>
<td>Other</td>
<td>__ yr. __ mo.</td>
<td>__ yr. __ mo.</td>
<td>☐</td>
</tr>
<tr>
<td>All Pediatric Subpopulations</td>
<td>0 yr. 0 mo.</td>
<td>16 yr. 11 mo.</td>
<td>☐</td>
</tr>
</tbody>
</table>

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)

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.

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. 9th 2011
Date

Confidential Not for Unauthorized Distribution

U.S. NDA: Tamiflu™—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

<table>
<thead>
<tr>
<th>NDA #</th>
<th>NDA Supplement #</th>
<th>If NDA, Efficacy Supplement Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>21087</td>
<td>062</td>
<td>New patient population (SE5); pediatric</td>
</tr>
<tr>
<td>21246</td>
<td>045</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Proprietary Name</th>
<th>Established/Proper Name</th>
<th>Dosage Form</th>
<th>Applicant</th>
<th>Agent for Applicant (if applicable)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TAMIFLU</td>
<td>oseltamivir phosphate</td>
<td>30, 45, 75 mg capsules and 6 mg/mL powder for oral suspension</td>
<td>Hoffmann-La Roche, Inc.</td>
<td>Genentech</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>RPM</th>
<th>Division</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elizabeth Thompson</td>
<td>DAVP</td>
</tr>
</tbody>
</table>

#### NDAs and NDA Efficacy Supplements:

- NDA Application Type: □ 505(b)(1) □ 505(b)(2)
- Efficacy Supplement: □ 505(b)(1) □ 505(b)(2)

(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.)

#### 505(b)(2) Original NDAs and 505(b)(2) NDA supplements:

- Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):
- Provide a brief explanation of how this product is different from the listed drug.

- This application does not reply upon a listed drug.
- This application relies on literature.
- This application relies on a final OTC monograph.
- This application relies on (explain)

For ALL (b)(2) applications, two months prior to EVERY action, review the information in the 505(b)(2) Assessment and submit the draft to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.

On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.

- No changes □ Updated □ Date of check:

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.

#### Actions

- Proposed action
- User Fee Goal Date is December 21, 2012
- Previous actions (specify type and date for each action taken) □ AP □ TA □ CR □ None

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1 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.

2 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).

Reference ID: 3235523

Version: 1/27/12
1. If accelerated approval or approval based on efficacy studies in animals, were promotional materials received?
   Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain.

2. Application Characteristics

   - Review priority: □ Standard  □ Priority
   - Chemical classification (new NDAs only):
     □ Fast Track
     □ Rolling Review
     □ Orphan drug designation
     □ Rx-to-OTC full switch
     □ Rx-to-OTC partial switch
     □ Direct-to-OTC

   - NDAs: Subpart H
     □ Accelerated approval (21 CFR 314.510)
     □ Restricted distribution (21 CFR 314.520)
   - BLAs: Subpart E
     □ Accelerated approval (21 CFR 601.41)
     □ Restricted distribution (21 CFR 601.42)
   - Subpart I
     □ Approval based on animal studies
   - BLAs: Subpart H
     □ Approval based on animal studies
   - REMS: □ MedGuide
     □ Communication Plan
     □ ETASU
     □ MedGuide w/o REMS
     □ REMS not required

   - Submitted in response to a PMR
   - Submitted in response to a PMC
   - Submitted in response to a Pediatric Written Request

   - Comments:

3. BLAs only: Ensure RMS-BLA Product Information Sheet for TBP and RMS-BLA Facility Information Sheet for TBP have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)

4. BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (approvals only)

5. Public communications (approvals only)
   - Office of Executive Programs (OEP) liaison has been notified of action
   - Press Office notified of action (by OEP)
   - Indicate what types (if any) of information dissemination are anticipated

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3 Answer all questions in all sections in relation 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.

Reference ID: 3235523
**Exclusivity**

- **Is approval of this application blocked by any type of exclusivity?**
  - No □ Yes

  - **NDAs and BLAs:** Is there existing orphan drug exclusivity for the “same” drug or biologic for the proposed indication(s)? 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.
    - No □ Yes
    - If yes, NDA/BLA # and date exclusivity expires:

  - **(b)(2) NDAs only:** Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)
    - □ No □ Yes
    - If yes, NDA # and date exclusivity expires:

  - **(b)(2) NDAs only:** Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)
    - □ No □ Yes
    - If yes, NDA # and date exclusivity expires:

  - **(b)(2) NDAs only:** Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)
    - □ No □ Yes
    - If yes, NDA # and date exclusivity expires:

  - **NDAs only:** Is this a single enunciation that falls under the 10-year approval limitation of 505(u)? (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.)
    - □ No □ Yes
    - If yes, NDA # and date 10-year limitation expires:

**Patent Information (NDAs only)**

- **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.
  - Verified □ Not applicable because drug is an old antibiotic.

  - **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.
    - 21 CFR 314.50(i)(1)(A) □ Verified
    - 21 CFR 314.50(i)(1) □ (ii) □ (iii)

  - **[505(b)(2) applications] If the application includes a paragraph III 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).**
    - □ No paragraph III certification
    - Date patent will expire

  - **[505(b)(2) applications] For each paragraph IV 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). (If the application does not include any paragraph IV certifications, mark “N/A” and skip to the next section below (Summary Reviews)).**
    - □ N/A (no paragraph IV certification) □ 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?

(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)?

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?

(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)?

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).
(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?

(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(i)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).

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).

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.

<table>
<thead>
<tr>
<th>CONTENTS OF ACTION PACKAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Copy of this Action Package Checklist</td>
</tr>
<tr>
<td>Officer/Employee List</td>
</tr>
<tr>
<td>List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (approvals only)</td>
</tr>
<tr>
<td>Documentation of consent/non-consent by officers/employees</td>
</tr>
<tr>
<td>Action Letters</td>
</tr>
<tr>
<td>Copies of all action letters (including approval letter with final labeling)</td>
</tr>
<tr>
<td>Labeling</td>
</tr>
<tr>
<td>Package Insert (write submission/communication date at upper right of first page of PI)</td>
</tr>
<tr>
<td>• Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.</td>
</tr>
<tr>
<td>• Original applicant-proposed labeling</td>
</tr>
<tr>
<td>• Example of class labeling, if applicable</td>
</tr>
</tbody>
</table>

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Fill in blanks with dates of reviews, letters, etc.
**Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling** (write submission/communication date at upper right of first page of each piece)

- Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.
  - December 21, 2012
- Original applicant-proposed labeling
  - June 21, 2012
- Example of class labeling, if applicable
  - N/A

**Labels** (full color carton and immediate-container labels) (write submission/communication date on upper right of first page of each submission)

- Most-recent draft labeling
  - N/A

**Proprietary Name**
- Acceptability/non-acceptability letter(s) (indicate date(s))
  - N/A
- Review(s) (indicate date(s))
  - N/A
- 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.

**Labeling reviews (indicate dates of reviews and meetings)**

<table>
<thead>
<tr>
<th>Administrative / Regulatory Documents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Administrative Reviews (e.g., RPM Filing Review/Memo of Filing Meeting) (indicate date of each review)</td>
</tr>
<tr>
<td>All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cnte</td>
</tr>
<tr>
<td>NDA (b)(2) Approvals Only: 505(b)(2) Assessment (indicate date)</td>
</tr>
<tr>
<td>NDAs only: Exclusivity Summary (signed by Division Director)</td>
</tr>
</tbody>
</table>

**Application Integrity Policy (AIP) Status and Related Documents**

- Applicant is on the AIP
  - No

<table>
<thead>
<tr>
<th>This application is on the AIP</th>
</tr>
</thead>
<tbody>
<tr>
<td>□ Yes</td>
</tr>
</tbody>
</table>

  | If yes, Center Director’s Exception for Review memo (indicate date) |
  | □ Yes | □ No |

  | If yes, OC clearance for approval (indicate date of clearance communication) |
  | □ Not an AP action |

**Pediatrics (approvals only)**
- Date reviewed by PeRC
  - N/A

  | If PeRC review not necessary, explain: supplements are new patient population therefore PREA not triggered |
  | □ Included |

  | Pediatric Page/Record (approvals only, must be reviewed by PERC before finalized) |
  | □ Included |

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5 Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

Reference ID: 3235523
<table>
<thead>
<tr>
<th>Section</th>
<th>Status</th>
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</thead>
<tbody>
<tr>
<td>Debarment certification (original applications only)</td>
<td>Verified, statement is acceptable</td>
</tr>
<tr>
<td>Outgoing communications (letters, including response to FDRR)</td>
<td>Included</td>
</tr>
<tr>
<td>Internal memoranda, telecons, etc.</td>
<td>Included</td>
</tr>
<tr>
<td>Minutes of Meetings</td>
<td></td>
</tr>
<tr>
<td>Regulatory Briefing (indicate date of mtg)</td>
<td>No mtg</td>
</tr>
<tr>
<td>If not the first review cycle, any end-of-review meeting (indicate date of mtg)</td>
<td>N/A or no mtg</td>
</tr>
<tr>
<td>Pre-NDA/BLA meeting (indicate date of mtg)</td>
<td>No mtg</td>
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<tr>
<td>EOP2 meeting (indicate date of mtg)</td>
<td>No mtg</td>
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<tr>
<td>Other milestone meetings (e.g., EOP2a, CMC pilots) (indicate dates of mtgs)</td>
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<tr>
<td>Advisory Committee Meeting(s)</td>
<td>No AC meeting</td>
</tr>
<tr>
<td>Date(s) of Meeting(s)</td>
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<td>48-hour alert or minutes, if available (do not include transcript)</td>
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**Decisional and Summary Memos**

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<tbody>
<tr>
<td>Office Director Decisional Memo (indicate date for each review)</td>
<td>None</td>
</tr>
<tr>
<td>Division Director Summary Review (indicate date for each review)</td>
<td>None</td>
</tr>
<tr>
<td>Cross-Discipline Team Leader Review (indicate date for each review)</td>
<td>None, December 13, 2012</td>
</tr>
<tr>
<td>PMR/PMC Development Templates (indicate total number)</td>
<td>None</td>
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</table>

**Clinical Information**

<table>
<thead>
<tr>
<th>Section</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Reviews</td>
<td></td>
</tr>
<tr>
<td>Clinical Team Leader Review(s) (indicate date for each review)</td>
<td>See CDTL review</td>
</tr>
<tr>
<td>Clinical review(s) (indicate date for each review)</td>
<td>November 28, 2012 (filing)</td>
</tr>
<tr>
<td>Social scientist review(s) (if OTC drug) (indicate date for each review)</td>
<td>December 10, 2012</td>
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<tr>
<td>Financial Disclosure reviews(s) or location/date if addressed in another review OR</td>
<td>See Clinical review (page 12)</td>
</tr>
<tr>
<td>If no financial disclosure information was required, check here and include a review/memo explaining why not (indicate date of review/memo)</td>
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<tr>
<td>Clinical reviews from immunology and other clinical areas/divisions/Centers (indicate date of each review)</td>
<td>None</td>
</tr>
<tr>
<td>Controlled Substance Staff review(s) and Scheduling Recommendation (indicate date of each review)</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Risk Management</td>
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<tr>
<td>REMS Documents and Supporting Statement (indicate date(s) of submission(s))</td>
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<tr>
<td>REMS Memo(s) and letter(s) (indicate date(s))</td>
<td>N/A</td>
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<tr>
<td>Risk management review(s) and recommendations (including those by OSE and CSS) (indicate date of each review and indicate location/date if incorporated into another review)</td>
<td>None, N/A, N/A</td>
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6 Filing reviews should be filed with the discipline reviews.
<table>
<thead>
<tr>
<th>Category</th>
<th>Review Dates</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DSI Clinical Inspection Review Summary(i)es</strong></td>
<td>None requested</td>
</tr>
<tr>
<td>Clinical Microbiology</td>
<td>None</td>
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<tr>
<td>Clinical Microbiology Team Leader Review(s)</td>
<td>None</td>
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<tr>
<td>Clinical Microbiology Review(s)</td>
<td>August 6, 2012 (filing)</td>
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<tr>
<td>Biostatistics</td>
<td>None</td>
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<tr>
<td>Statistical Division Director Review(s)</td>
<td>None</td>
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<tr>
<td>Statistical Team Leader Review(s)</td>
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<td>Statistical Review(s)</td>
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<td>Clinical Pharmacology</td>
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<td>Clinical Pharmacology Division Director Review(s)</td>
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<td>Clinical Pharmacology Team Leader Review(s)</td>
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<td>Clinical Pharmacology review(s)</td>
<td>August 3, 2012 (filing)</td>
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<tr>
<td>DSI Clinical Pharmacology Inspection Review Summary</td>
<td>None</td>
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<tr>
<td>Nonclinical</td>
<td>None</td>
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<tr>
<td>Pharmacology/Toxicology Discipline Reviews</td>
<td></td>
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<tr>
<td>ADP/T Review(s)</td>
<td>None</td>
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<tr>
<td>Supervisory Review(s)</td>
<td>None</td>
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<tr>
<td>Pharm/tox review(s), including referenced IND reviews</td>
<td>None</td>
</tr>
<tr>
<td>Review(s) by other disciplines/divisions/Centers requested by P/T reviewer</td>
<td>None</td>
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<tr>
<td>Statistical review(s) of carcinogenicity studies</td>
<td>No carc</td>
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<tr>
<td>ECAC/CAC report/memo of meeting</td>
<td>None</td>
</tr>
<tr>
<td>DSI Nonclinical Inspection Review Summary</td>
<td>None requested</td>
</tr>
</tbody>
</table>
### Product Quality

<table>
<thead>
<tr>
<th>Discipline Review</th>
<th>None</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Product Quality Discipline Reviews</strong></td>
<td></td>
</tr>
<tr>
<td>• ONDQA/OBP Division Director Review(s) <em>(indicate date for each review)</em></td>
<td>None</td>
</tr>
<tr>
<td>• Branch Chief/Team Leader Review(s) <em>(indicate date for each review)</em></td>
<td>None</td>
</tr>
<tr>
<td>• Product quality review(s) including ONDQA biopharmaceutics reviews <em>(indicate date for each review)</em></td>
<td>None</td>
</tr>
<tr>
<td><strong>Microbiology Reviews</strong></td>
<td></td>
</tr>
<tr>
<td>□ NDAs: Microbiology reviews *(sterility &amp; pyrogenicity) <em>(OPS/NDMS)</em> <em>(indicate date for each review)</em></td>
<td>Not needed</td>
</tr>
<tr>
<td>□ BLAs: Sterility assurance, microbiology, facilities reviews <em>(OMPQ/MAPCB/BMT)</em> <em>(indicate date for each review)</em></td>
<td></td>
</tr>
<tr>
<td>**Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <em>(indicate date of each review)</em></td>
<td>None</td>
</tr>
<tr>
<td><strong>Environmental Assessment</strong> <em>(check one)</em> <em>(original and supplemental applications)</em></td>
<td></td>
</tr>
<tr>
<td>□ Categorical Exclusion <em>(indicate review date)</em> <em>(all original applications and all efficacy supplements that could increase the patient population)</em></td>
<td>August 6, 2012</td>
</tr>
<tr>
<td>□ Review &amp; FONSI <em>(indicate date of review)</em></td>
<td></td>
</tr>
<tr>
<td>□ Review &amp; Environmental Impact Statement <em>(indicate date of each review)</em></td>
<td></td>
</tr>
<tr>
<td><strong>Facilities Review/Inspection</strong></td>
<td></td>
</tr>
<tr>
<td>□ NDAs: Facilities inspections <em>(include EER printout)</em> <em>(date completed must be within 2 years of action date)</em> <em>(only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites)</em></td>
<td></td>
</tr>
<tr>
<td>□ BLAs: TB-EER <em>(date of most recent TB-EER must be within 30 days of action date)</em> <em>(original and supplemental BLAs)</em></td>
<td></td>
</tr>
<tr>
<td><strong>NDAs: Methods Validation</strong> <em>(check box only, do not include documents)</em></td>
<td></td>
</tr>
</tbody>
</table>

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7 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.
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/s/

ELIZABETH G THOMPSON
12/21/2012
Maria

Here is the Division's recommendations/revisions for the

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
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/s/

ELIZABETH G THOMPSON
12/20/2012
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
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/s/

ELIZABETH G THOMPSON
12/20/2012
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
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elizabeth.thompson@fda.hhs.gov
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
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/s/

ELIZABETH G THOMPSON
12/20/2012
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
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/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
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/s/

ELIZABETH G THOMPSON
12/14/2012
Maria-

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

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]
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
On Thu, Dec 13, 2012 at 12:22 PM, Thompson, Elizabeth <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
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Silver Spring, MD 20993
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elizabeth.thompson@fda.hhs.gov

Reference ID: 3231475

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

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
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
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/s/

ELIZABETH G THOMPSON
12/14/2012
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.

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

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/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

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.

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 peds efficacy supplement.

Consider revising the sentences after the paragraph that begins 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.

Reference ID: 3211821
PLEASE REPLY BY EMAIL (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
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/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) 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}
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/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) 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}
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/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) 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

Reference ID: 3181818
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/s/

ELIZABETH G THOMPSON
08/29/2012
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 0 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 \( n \) weeks of post-conceptual age. Please provide a summary of available data in infants less than \( n \) 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)**

   - 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

Reference ID: 3176889
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,
defered, 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

Reference ID: 3176889
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/s/

DEBRA B BIRNKRANT
08/20/2012
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
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/s/

ELIZABETH G THOMPSON
08/01/2012
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.
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/s/

ELIZABETH G THOMPSON
07/17/2012
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 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

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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.

Sincerely,

{See appended electronic signature page}

Elizabeth Thompson, M.S.  
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/s/

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07/02/2012